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(71) Applicant *(for all designated States except US)*: **SUNTORY LIMITED** [JP/JP]; 1-40, Dojimahama 2-chome, Kita-ku, Osaka-shi, Osaka 530-8203 (JP).

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(75) Inventors/Applicants *(for US only)*: **TAKEMOTO, Naohiro** [JP/JP]; 4-5-305, Nishichujo-cho, Ibaraki-shi, Osaka 567-0887 (JP). **ANNOURA, Hirokazu** [JP/JP]; 16-8, Kitashinotani, Chohoji, Nagaokakyo-shi, Kyoto 617-0812 (JP). **MURAYAMA, Norihito** [JP/JP]; 9-5-507, Yamazaki 1-chome, Shimamoto-cho, Mishima-gun, Osaka 618-0001 (JP).

(74) Agent: **KUSAMA, Osamu**; KUSAMA PATENT OFFICE, 7F, Iwata Bldg., 5-12, Iidabashi 4-chome, Chiyoda-ku, Tokyo 102-0072 (JP).

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Published:
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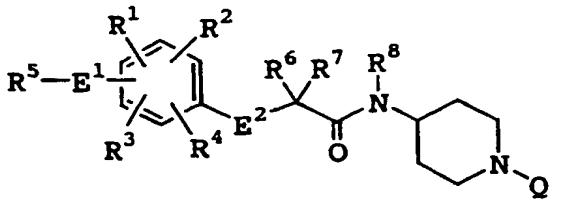
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMINOPHENOXYACETAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITION CONTAINING THEREOF

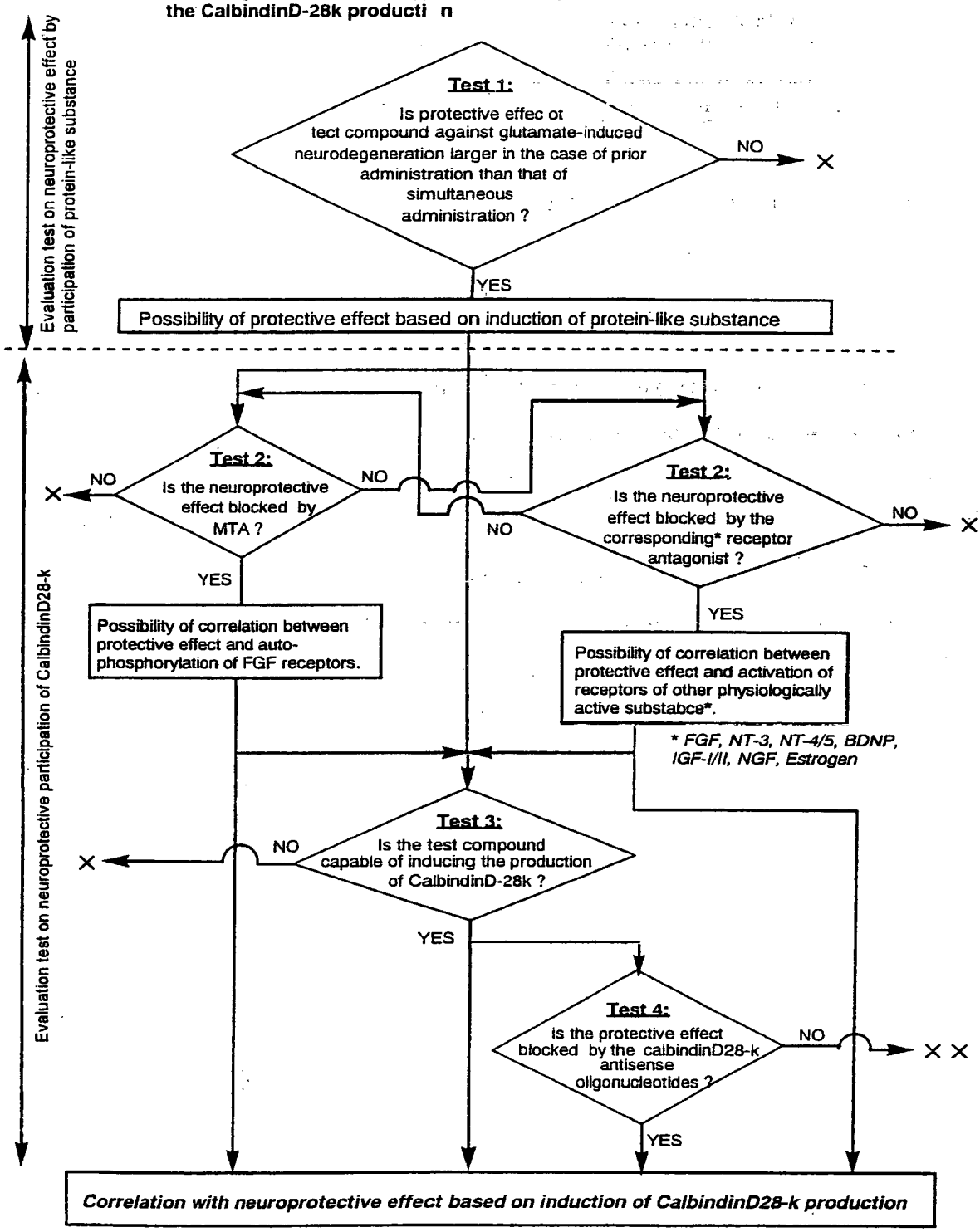


(I)

(57) Abstract: There is provided an aminophenoxyacetamide derivative of the formula (I): wherein, R^1 to R^4 are, independent from each other, hydrogen atom; optionally substituted alkyl group; E^1 is $-NR^4-$ and E^2 is oxygen atom or $-NR^{10}$; Q is group -X-Y-Q' (X and Y are connecting bond; X is alkylene or alkenylene group, etc.; Y is selected from the groups consisting of C=O, NHC(=O), C(=O)NH, etc.; Q' is hydrogen atom or pheny, pyridyl groups which may be substituted, etc.),or a pharmaceutically acceptable salt thereof.These compounds have neuroprotective effect by introducing the CalbindinD-28k, one of Ca^{2+}-binding proteins.11

WO 01/79170 A2

S lecting m thod f neuroprote tive compound based on induction of the CalbindinD-28k producti n



×: Compound out of selecdtion.

××: Compound produces CalbindinD-28k, but main neuroprotective effect is correlated with something else.

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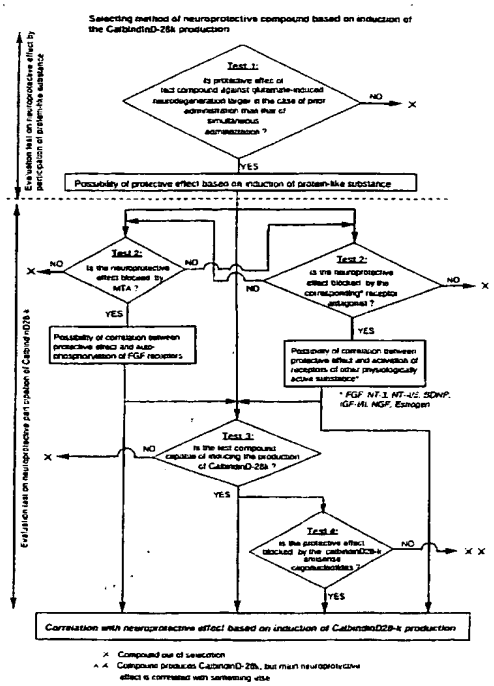
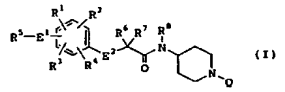
[Continued on next page]

(54) Title: AMINOPHENOXYACETAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITION CONTAINING THEREOF





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13 June 2002

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 01/03198

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/15 C07D211/58 C07D417/04 A61K31/4468 A61P25/00
G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 23076 A (SUNTORY LTD ;URAMOTO HIROSHI (JP); ANNOURA HIROKAZU (JP); TAKEMOTO) 27 April 2000 (2000-04-27) the whole document	1-18
A	EP 0 982 026 A (HOFFMANN LA ROCHE) 1 March 2000 (2000-03-01) example 79	1,4-16, 19,20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2002	22.03.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Pellegrini, P

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BOUILLON R ET AL: "Antagonistic activity of 24-oxa-analogs of vitamin D" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 60, no. 6, 1 June 1995 (1995-06-01), pages 484-490, XP004026517 ISSN: 0039-128X paragraph "intrinsic activity" page 487, right-hand column ---	1,4-16, 19,20
A	MCMAHON ANNE ET AL: "Calbindin-D28k buffers intracellular calcium and promotes resistance to degeneration in PC12 cells." MOLECULAR BRAIN RESEARCH, vol. 54, no. 1, February 1998 (1998-02), pages 56-63, XP001064171 ISSN: 0169-328X abstract page 59, column 2, paragraph 3 page 63, column 1, paragraph 2 ---	16-18
A	NG MAY C ET AL: "The neurotoxin MPTP increases calbindin-D-28k levels in mouse midbrain dopaminergic neurons." MOLECULAR BRAIN RESEARCH, vol. 36, no. 2, 1996, pages 329-336, XP001064172 ISSN: 0169-328X abstract ---	16-18
A	MASUMURA MAKOTO ET AL: "Selective induction of fibroblast growth factor receptor-1 mRNA after transient focal ischemia in the cerebral cortex of rats." NEUROSCIENCE LETTERS, vol. 213, no. 2, 1996, pages 119-122, XP001064173 ISSN: 0304-3940 abstract -----	16-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 01/03198

Box I Observations where certain claims wer found uns archable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 19-21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19-21

Claims 19-21 relate to neuroprotective compounds defined by reference to a desirable characteristic or property, namely being selected by the method according ro any one of claims 16 to 18.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for the compounds claimed in claims 1-3, on which a search has already been performed.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the subject-matter of claims 19-21 going beyond the above-mentioned compounds is impossible. Consequently, no search has been performed on these claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

IN ERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 01/03198

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0023076 A	27-04-2000	AU 6122699 A	08-05-2000
		CN 1287487 T	14-03-2001
		EP 1045693 A1	25-10-2000
		HU 0100819 A2	28-08-2001
		WO 0023076 A1	27-04-2000
EP 0982026 A	01-03-2000	EP 0982026 A2	01-03-2000
		AU 4453799 A	04-05-2000
		BR 9903779 A	19-09-2000
		CN 1248439 A	29-03-2000
		HR 990256 A1	30-04-2000
		HU 9902737 A2	28-06-2000
		JP 2000109429 A	18-04-2000
		NO 993948 A	21-02-2000
		PL 334949 A1	28-02-2000
		TR 9902015 A2	21-03-2000
		US 6184236 B1	06-02-2001
		ZA 9905212 A	18-02-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
KUSAMA PATENT OFFICE
Attn. Kusama, Osamu
7F Iwata Bldg., 5-12, Iidabashi
4-chome, Chiyoda-ku
Tokyo 102-0072
JAPAN

RECEIVED WITH THANKS
01.8.8
KUSAMA PATENT OFFICE

INVITATION TO FURNISH NUCLEOTIDE AND/OR AMINO ACID SEQUENCE LISTING COMPLYING WITH WIPO STANDARD ST25

(PCT Rule 13ter.1(a) and (c) and Administrative Instructions, Section 208 and Annex C)

	Date of mailing *(day/month/year)* 30/08/2001
Applicant's or agent's file reference SN-48	**REPLY DUE** within 1 months/~~days~~ from the above date of mailing
International application No. PCT/JP 01/ 03198	International filing date *(day/month/year)* 13/04/2001
Applicant SUNTORY LIMITED	

1. The applicant is hereby **invited**, within the time limit indicated above, to furnish to this Authority:

   [X] a nucleotide and/or amino acid sequence listing **in written form** complying with the standard provided for in Annex C of the Administrative Instructions, accompanied by a **statement** to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

   [ ] a **statement** to the effect that the sequence listing in written form, already furnished to this Authority, does not go beyond the disclosure in the international application as filed.

   [X] a nucleotide and/or amino acid sequence listing **in computer readable form** complying with the standard provided for in Annex C of the Administrative Instructions, accompanied by a **statement** that the information recorded in computer readable form is identical to the written sequence listing.

   [ ] a **statement** that the information recorded in computer readable form (that computer readable form having already been furnished to this Authority) is identical to the written sequence listing.

2. **Failure to comply with this invitation** may result in this Authority not carrying out the international search to the extent that no meaningful search can be carried out.

3. Further observations (if necessary):

IMPORTANT REMARK
The statements are legally required [See Suppl.No.2 to Official Journal No.11/1998 (page 14, ψ 37 & 40 and page 64, ψ III.2)]

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Zorka Bota-Madsen Z. Bota-Madsen

Form PCT/ISA/225 (July 1998)

Office Européen des Br vets DG1
Europäisches PatentAmt DG1
Europ an Patent Office DG1

***S**torage and **R**etrieval of **A**mino acid and **N**ucleotide **D**ata*

Ms. Zorka Bota-Madsen
P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Fax : + 31 70 340 39 92 **Tel. : + 31 70 340 23 93**

ANNEX

Dear applicant/representative,

Present application discloses amino acid/nucleotide sequences.**(see description, claims and figures)**

According to Supplement 2 to the Official Journal Nr.11/98 of the EPO [& Rule 5.2. PCT], if nucleotide / amino acid sequences **are disclosed** in a European/International patent application, the description shall contain a *sequence listing* complying with **WIPO standard ST. 25.**

The Sequence Listing is required for the explicit sequences given in the description, claims and figures of the present application.
Please note that the sequences which are not identical to the sequences disclosed in the prior art (fragments and/or modifications) should be given in the Sequence Listing.

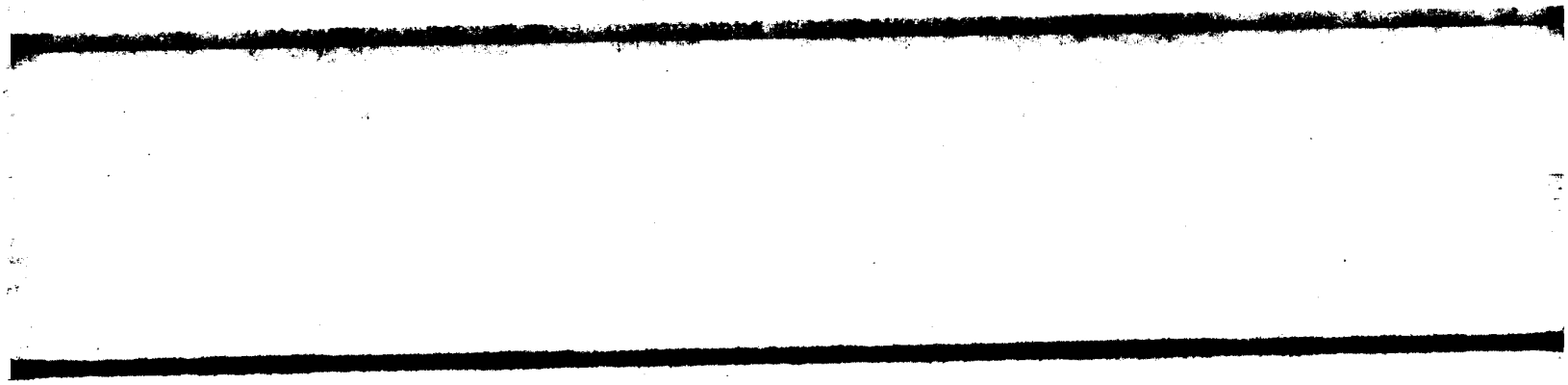
The expressions nucleotide and amino acid sequences mean an unbranched of **ten or more** contiguous nucleotides and an unbranched sequence of **four or more** contiguous amino acids. Nucleotide sequences shorter than 10 contiguous nucleotides and amino acids sequences shorter than 4 residues must not be included in a sequence listing.

The ISA hereby invites the applicant to submit a sequence listing, with appropriate annotations for each sequence [where applicable], both on paper and in computer readable form, accompanied by the appropriate statements.
Relating to this, we remind you that if these requirements are not met or not met in due time, the EPO does not perform the international search where a meaningful search cannot be carried out (Rule 13ter.1(c)PCT). In this case the international search report is replaced in full or in part by the statement under Article 17(2)(a)(ii)PCT.
Moreover Rule 13ter(f)prescribes that a subsequently filed sequence listing, which is not a correction within the meaning of rule 26.4 PCT and which is not a rectification within the meaning of Rule 91.1.PCT of a sequence listing, shall not form part of the international application. In accordance herewith, the furnishing of a subsequently filed sequence listing does not give rise to an opportunity either to amend the description, claims and figures with a view to refer to said subsequently filed sequence listing or add it to the application as originally filed. The subsequently furnished listing will therefore normally not be forwarded to the international Bureau for publication purposes.

We strongly recommend the applicant to use the **PatentIn** software to submit the sequence listing. (If problems arise with the download of the PatentIn software, a CD-ROM copy can be obtained through Ms. van Laar-Rabelink -Room 08-37, Tel +31 70 340 4440 ; Fax : +31 70 340 3992 ; E-mail : epoline@epo.org), free of charge; Internet: http://www.european-patent-office.org.

The computer readable form of the Sequence Listing in ASCII format (text only) is mandatory. For further questions do not hesitate to contact us.

Please send sequence listing on paper and in computer-readable form preferably to the European Patent Office, Strand Program, Directorate Biotechnology (Dir 1212), Ms.Z.Bota-Madsen, Room S 02 N 06, Patentlaan 2, NL 2288 EE Rijswijk, The Netherland



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DESCRIPTION

AMINOPHENOXYACETAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITION CONTAINING THEREOF

TECHNICAL FIELD

The present invention relates to cerebral functional or organic disorders improving and treating agents containing aminophenoxyacetamide derivatives and pharmaceutically acceptable salt thereof as an active ingredient, having neuroprotective effect by inducing the production of CalbindinD-28k, one of Ca^{2+}-binding proteins, and to the methods for selecting these neuroprotective aminophenoxyacetamide derivatives. More specifically, the present invention relates to the therapeutic and improving agents for various cerebral dysfunction due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis. Furthermore, the present invention relates to therapeutic and improving agents for various cerebral organic disorders due to senile dementia, sequelae of cerebral injury, or surgical operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and Huntington's disease, etc.

BACKGROUND ART

It is considered that the progressive and delayed death of nerve cells, observed in cerebral injury and cerebrovascular disease such as intracerebral hemorrhage, transient cerebral ischemia, and cerebral infarction, is mainly caused by the increase of the intracellular Ca^{2+} concentration, the various factors of which are related to signal transduction to cause, for example, the abnormal activation of receptors by over releasing glutamate which is internal excitability, the activation of ion

channels, and the induction of reactive oxygen species/free radicals. [F. B. Meyer, *Brain Res. Rev.*, 14, 227 (1989); E. Boddeke et al., *Trends Pharmacol. Sci.*, 10, 397 (1989); J. M. McCall et al., *Ann. Rep. Med. Chem.*, 27, 31 (1992)].

From these points of view, antagonists for glutamate receptors, calcium channel blockers, antioxidants and so on have been applied for medicaments of preventing or suppressing the neurodegeneration. However, these clinically used medicaments suppress only a few pathways relating to the increase of the cellular Ca^{2+} concentration, and therefore are not yet sufficient enough for preventing or suppressing the neurodegeneration.

On the contrary, the internal production of CalbindinD-28k is induced by activation of receptors for many physiologically active substance's such as FGF, NT-3, NT-4/5, BDNF, IGF-I/II, PDGF, estrogen and so on, and as well as by activation of FGF receptor, which is one of nerve growth factor receptors [C. V.-Abejon et el., *Neuron*, 15, 105 (1995); A. Silva et al., *Brain Res. Bull.*, 1, 35 (2000)]. And CalbindinD-28k, one of Ca^{2+}-binding proteins and mainly distributed in vulnerable site against ischemic disorders in the central nervous system, which is known to show buffer action against the increase of intracellular Ca^{2+} concentration. [A. M. Lacopino et al., *Neurodegeneration*, 3, 1 (1994); M. P. Mattson et al., *Neuron*, 6, 41 (1991)]

Accordingly, it is expected to achieve sufficient neuroprotective effects against the increase of intracellular Ca^{2+} concentration caused by any kinds of pathways if CalbindinD-28k, one of the Ca^{2+}-binding proteins per se, can be supplied in a cell. Namely, it is expected that medicaments containing CalbindinD-28k would be extremely effective therapeutic and improving agents against cerebral functional and due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and

cerebral arteriosclerosis. It is also expected to be effective against cerebral dysfunction due to cerebral ischemic disorders due to sequelae of senile dementia, cerebral injury and surgical operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

However, it is very difficult and therefore it is not likely to administer the CalbindinD-28k protein directly into the desirable site in the central nervous system of a body in view of the limitations existing in the pharmacological and pharmaceutical methodology because CalbindinD-28k itself is an unstable macro molecular weight protein having 28 Kd (Kilo Dalton) of molecular weight.

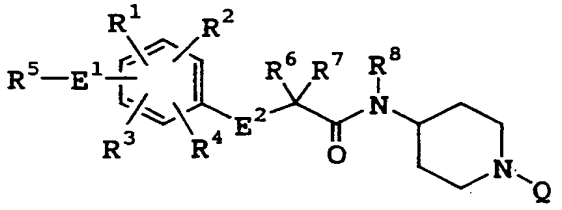
On the other hand, the lower molecular weight compounds capable of including the production of CalbindinD-28k protein can be easily prepared into the various kinds of pharmaceutical compositions by the conventional technique. Therefore, these lower molecular weight compounds would induce the production of the neuroprotective CalbindinD-28k protein once easily administered into a body, showing the buffering action against the increase of the intracellular Ca^{2+} concentration. That is, these lower molecular weight compounds can be effective pharmaceutical compounds for improving and treating cerebral functional and organic disorders.

Under these circumstances, one objective of the present invention is to select and to provide the lower molecular-weight neuroprotective compounds capable of inducing the production of CalbindinD-28k, one kind of Ca^{2+}-binding proteins, via phosphorylation of receptors of various physiologically active substances, as well as to provide the pharmaceutical compositions of low toxicity in suitable preparations such as intravenous injectable solution.

The other objective of the present invention is to provide the therapeutic and improving agents for cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as sequelae of senile dementia, cerebral injury, or surgical operation, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

DISCLOSURE OF THE INVENTION

As one aspect of the present invention, it is provided aminophenoxyacetamide derivatives represented by the following formula (I):



(I)

wherein,

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom or lower alkyl group which may be substituted;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom or lower alkyl group which may be substituted;

E^1 is group $-NR^9$ (in which, R^9 is hydrogen atom or alkyl group which may be substituted);

E^2 is oxygen atom or group $-NR^{10}$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted or aralkyl group which may be substituted); Q is a group of -X-Y-Q', in which X is a connecting bond, lower alkyl group, lower alkenyl group or lower alkynyl group; Y is a connecting bond, or a group selected from the groups consisting of C=O, C(=O)NH, NHC(=O), -O-, -S-, CH(OH), -O-CH(OH), and -O-

CH2-CH(OH), in which hydrogen atom of amido group may be substituted with lower alkyl group; and Q' is hydrogen atom or a cyclic group selected from the groups consisting of aryl group, heteroaryl group, saturated or unsaturated cyclic hydrocarbon group, and satuated or unsaturated heterocyclic group, wherein one or more of the hydrogen atom in the cyclic group of Q' may be substituted;

provided that X and Y are both connecting bond then Q' is not hydrogen atom; or provided that one of X and Y is other than connecting bond then E2 is the group -O- and all of the groups of R1, R2, R3 and R4 are not hydrogen atom;
or a pharmaceutically acceptable salt thereof.

In the description of a lower alkyl group may be specifically a straight or branched alkyl group of the number of carbon atoms from C_1 to C_6, for example, methyl, ethyl, n-propyl, isopropyl and so on and more preferably, methyl or ethyl. In the description of lower alkenyl group may be specifically C_1 to C_6 alkenyl group, and lower alkynyl may be specifically C_1 to C_6 alkynyl group.

Furthermore, the present invention provides the aminophenoxyacetamide derivatives of the formula (I), in which;

R^1, R^2, R^3 and R^4 all are methyl group;

when E^1 is oxygen atom; E^2 is the group $-NR^9$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted or aralkyl group which may be substituted); or when E^1 is group $-NR^{10}$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted); E^2 is oxygen atom;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom or lower alkyl group;

Q is group -X-Y-Q' (in which, Q' is hydrogen atom, phenyl group which may be substituted, pyridyl group which may be substituted, quinolyl group which may be substituted, isoquinolyl group which may be substituted; benzothiazole group which may be substituted or benzimidazole group which may be substituted;or pharmaceutically acceptable salts thereof.

More specifically, the following compound groups (1) to (4) are the specific embodiments of the aminophenoxyacetamide derivatives of the formula (I) of the present invention having the excellent effect.

(1) The aminophenoxyacetamide derivatives claimed in claim 1, wherein;

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; or alkyl group which may be substituted;

R^5 is hydrogen atom or alkyl group which may be substituted; E^1 is -NH-;

E^2 is oxygen atom;

or pharmaceutically acceptable salts thereof.

(2) The aminophenoxyacetamide derivatives claimed in claim 1, wherein;

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; or alkyl group which may be substituted;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 and E^2 are -NH-;

or pharmaceutically acceptable salts thereof.

(3) The aminophenoxyacetamide derivatives claimed in claim 2, wherein;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

when X is connecting bond, Y is -CONH-; or when X is -CONH-, Y is connecting bond;

Q' is phenyl group which may be substituted;

or pharmaceutically acceptable salts thereof.

(4) The aminophenoxyacetamide derivatives claimed in claim 2, wherein;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

X is connecting bound or alkylene group and Y is one of the groups consisting of -CH(OH)-, -O-CH(OH)-, and -O-CH_2-CH(OH)-;

Q' is phenyl group which may be substituted;

or pharmaceutically acceptable salts thereof.

According to the present inventor's investigations, it is confirmed that the aminophenoxyacetamide derivatives represented by the formula (I) effectively induced the production of CalbindinD-28K in low concentration and possessed excellent neuroprotective effect. Further, these compounds are also confirmed to have high safety margin, and are suitable for preparation of various kinds of pharmaceutical compositions.

Therefore, as a further embodiment, the present invention provides an improving and therapeutic agent for the cerebral functional and organic disorders containing aminophenoxyacetamide derivatives represented by the formula (I) or pharmaceutically acceptable salt thereof, as an active ingredient.

As another embodiment, the present invention provides effective and simple method of selecting (screening) lower molecular weight compounds capable of inducing the production of the CalbindinD-28k, one of Ca^{2+}-binding proteins.

The method of selecting low molecular weight compounds consists of several evaluation tests mentioned below;

(1) Evaluation test to compare the neuroprotective effect of the test compounds against glutamate-induced neurodegeneration, between the administration thereof prior to the glutamate addition and the simultaneous administration thereof.

(2) The test to confirm whether or not the aforementioned neuroprotective effect is neuroprotective through phosphorylation of receptors for various physiologically active substances. These tests are conducted by the antagonistic effect of the inhibitors for each of the receptors such as FGF NT-3, NT-4/5, BDNF, IGF-I/II, PDGF, or estrogen, and MTA (5-Deoxy-5-Methylthioadenosine), which specifically inhibits autophosphorylation of FGF receptor.

(3) Evaluation test of inducing capability for each test compounds to produce CalbindinD-28k.

(4) Confirmation test for neuroprotective effect of CalbindinD-28k by the inhibition using its antisense oligonucleotide.

By the above stated evaluation tests, effective compounds having the following features can be selected.

Evaluation test (1):

This test is to evaluate whether the test compounds have neuroprotective effect against glutamate induced neurodegeneration, by administrating such testing compounds before or simultaneously along with the glutamate to induce the neuronal cell injury.

If the test compound shows greater neuroprotective effect against neurodegeneration induced by glutamate administration in case of pre-treatment than that in case of simultaneously

treatment, then the compound may possess effect of inducing protein like substance, which shows neuroprotective effect. Therefore, the compound possessing neuroprotective effect based on the protein like substance induced, including CalbindinD-28k, one of Ca^{2+}-binding proteins, is selected by this evaluation test.

Evaluation test (2):

In the case where neuroprotective effect disappears by the administration of inhibitors to receptors such as FGF, NT-3, NT-4/5, BDNF, IGF-I/II, PDGF and estrogen, then it is confirmed that such neuroprotective effect is caused by the activation of these receptors. Furthermore, in the living cell, MTA (5-Deoxy-5-Methylthioadenosine) specifically inhibits autophosphorylation of FGF receptors. Inhibition of neuroprotective activity by the treatment with MTA (specific inhibitor for self-physpholylation of FGF receptors) confirms that such neuroprotective effect involves phosphorylation of FGF receptors. Therefore, this evaluation test would select the compounds which neuroprotective ffect is expressed by the activation of receptors of various physiologically active substances and through phosphorylation of FGF receptor.

Evaluation test (3):

The compound having effect of inducing CalbindinD-28k production would be selected by this evaluation test.

Evaluation test (4):

It is necessary for the protective protein to be produced via the signal transduction of cells through the phosphorylation of receptors of various physiologically active substances to provide the neuroprotective effect of the compounds, and the CalbindinD-28k is one of that protective proteins. Therefore,

with this evaluation test, the compound which has neuroprotective activity due to the CalbindinD-28k production, is inhibited by using CalbindinD-28k antisense. In this test, the compound having neuroprotective effect is confirmed based on the CalbindinD-28k produced.

The present invention provides effective and simple selecting method of lower molecular weight neuroprotective compounds based on CalbindinD-28k production induced, by using all of the evaluation tests, or using the combination of evaluation tests (1) and (2), evaluation tests (1), (2) and (3), evaluation tests (1) and (3) or evaluation tests (1), (3) and (4).

Figure 1 shows the flow chart of the selecting methods of the present invention to show the overview of selecting method of lower molecular weight compounds possessing neuroprotective effect based on CalbindinD-28k production induced, by combining aforementioned evaluation tests.

In accordance with the selecting methods of the present invention, the compounds specifically described in the description of the present invention is selected as lower molecular weight compounds possessing the inducing effect on the production of CalbindinD-28k, one of Ca^{2+}-binding protein. However, these selecting methods can be applied to selecting various compounds possessing neuroprotective effect based on activation of physiologically active substance's receptors and CalbindinD-28k production inducing effect involving autophosphorylation of FGF receptor, and are not limited to the selection of the compounds described in this specification.

BRIEF DESCRIPTION OF DRAWING

Figure 1 shows the flow chart of the selecting methods of

lower molecular weight compounds possessing neuroprotective effect based on production of CalbindinD-28k induced of the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

The aminophenoxyacetamide derivatives of the present invention include aminophenoxyacetamides, aminoanilinoacetamides, aminothiophenoxyacetamides, oxyanilinoacetamides and thioanilinoacetamides. Therefore, "aminophenoxyacetamide derivatives" in this specification include all the derivatives stated above as long as not stated otherwise.

In the aminophenoxyacetamide derivatives of the formula (I) provided by the present invention with reference to various substitution group of R^1 to R^{10}, "halogen atom" includes fluorine atom, chlorine atom and bromine atom.

The term "alkoxy group" stands for a straight-chained or branched-chained C_1-C_5 alkoxy group, and may include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy and the like.

The term "alkyl group which may be substituted" stands for a straight-chained or branched-chained C_1-C_5 alkyl group which may be halogen-substituted, and may include, for example, methyl, ethyl, propyl, trifluoromethyl group, and the like.

The "aryl", a part of the term "aryl group which may be substituted", stands for C_4-C_{14} aryl group containing at least one hetero atom(s) such as nitrogen and oxygen atom(s). Examples of the preferred aryl group include phenyl, pyridyl and naphthyl. The suitable substituents of said aryl group include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group having 1 to 5 carbon atoms such as methoxy group and ethoxy

group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl.

The "aralkyl", a part of the term "aralkyl group which may be substituted", stands for C_5-C_{12} aralkyl group containing at least one hetero ring atom(s) such as nitrogen and oxygen atom(s). The examples include benzyl, phenethyl, pyridylmethyl, and pyridylethyl.

The suitable substituents of said aralkyl group include halogen atoms such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy group and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl.

The "aryl", a part of the term "aryl group which may be substituted" represented as "Q", stands for C_4-C_{14} aryl group which may contain at least one hetero atom(s) such as nitrogen and oxygen atom(s). The examples include phenyl, pyridyl and naphthyl. The suitable substituents of said aryl group include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group having 1 to 5 carbon atoms such as methoxy group and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl. Furthermore, these substituents may also include a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as fluorine atom, chlorine atom and bromine atom.

The "alkylene", a part of the term "alkylene group which may b substituted by hydroxyl group", refers to the substituets "X" and "Y", and preferably represents a straight-chained or

branched-chained C_1-C_6 alkylene group such as methylene, methylmethylene, ethylene, trimethylene, tetramethylene, cyclopropylmethylene and the like.

The term "cycloalkylene" preferably stands for C_3-C_6 cycloalkylene and may include 1,1-cyclopropylene, 1,2-cyclopropylene, 1,1-cyclobutylene, 1,1-cyclopentylene, 1,1-cyclohexylene and the like. Among them, 1,1-cyclopropylene and 1,2-cyclopropylene are more preferable.

The "alkenylene", a part of the term "alkenylene group which may be substituted by lower alkyl group", may include C_2-C_4 alkenylene such as vinylene, and butadiene, and vinylene is preferably used. The lower alkyl group, which is substituent of alkenylene group, may be methyl, ethyl, propyl, isopropyl and the like.

The term "connected bond" with reference to "X" and "Y" means direct bond. Therefore, if "X" and/or "Y" are connected bond, two adjacent substituents of "X" and/or "Y" are connected directly, and these substituents do not exist as "X" and/or "Y".

The suitable substituents represented as "Q'" for "phenyl group which may be substituted", "phenoxy group which may be substituted", "benzoyl group which may be substituted", "pyridyl group which may be substituted", "quinolyl group which may be substituted", "isoquinolyl group which may be substituted", "benzothiazole group which may be substituted" and "benzimidazolyl group which may be substituted", may include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy, ethoxy group and so on. Furthermore, these substituents may also include a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as methyl, ethyl, trifluoromethyl and the like.

It is understood that when the aminophenoxyacetamide derivatives of the formula (I) of the present invention exist in the isomer forms, each isomers *per se*, as well as the isomeric mixture, shall be included in the compounds of the present invention. Namely, the structural isomers may exist due to the substituents on the benzene ring. Furthermore, optical isomers may exist due to the asymmetric carbon atom of the hydroxy substituted "X" or "Y" of alkylene group. These isomers shall be included within the scope of the compounds of the present invention.

The aminophenoxyacetamide derivatives of the formula (I) include the compounds (Ia), (Ib) (Ic) and (Id) obtained by the synthetic process mentioned latter. For example, these compounds may be prepared by the following.

The compound (IV), obtained by the reaction of the compound (II) with the ester derivative (III), is hydrolyzed to convert into the carboxylic acid derivative (V). Furthermore, the compound (VIII) is obtained by the reaction of the amine derivative (VI) with the compound (VII), and the protecting group of the compound (VIII) is removed to obtain the amine derivative (IX). Then, the obtained compound (V) is converted into amide compound (X) by the condensation reaction with the compound (IX). Further, the protecting group in the compound (X) thus obtained is removed to obtain compound (Ia), the compound of formula (I) in the Claim 1 of the present invention (Process 1).

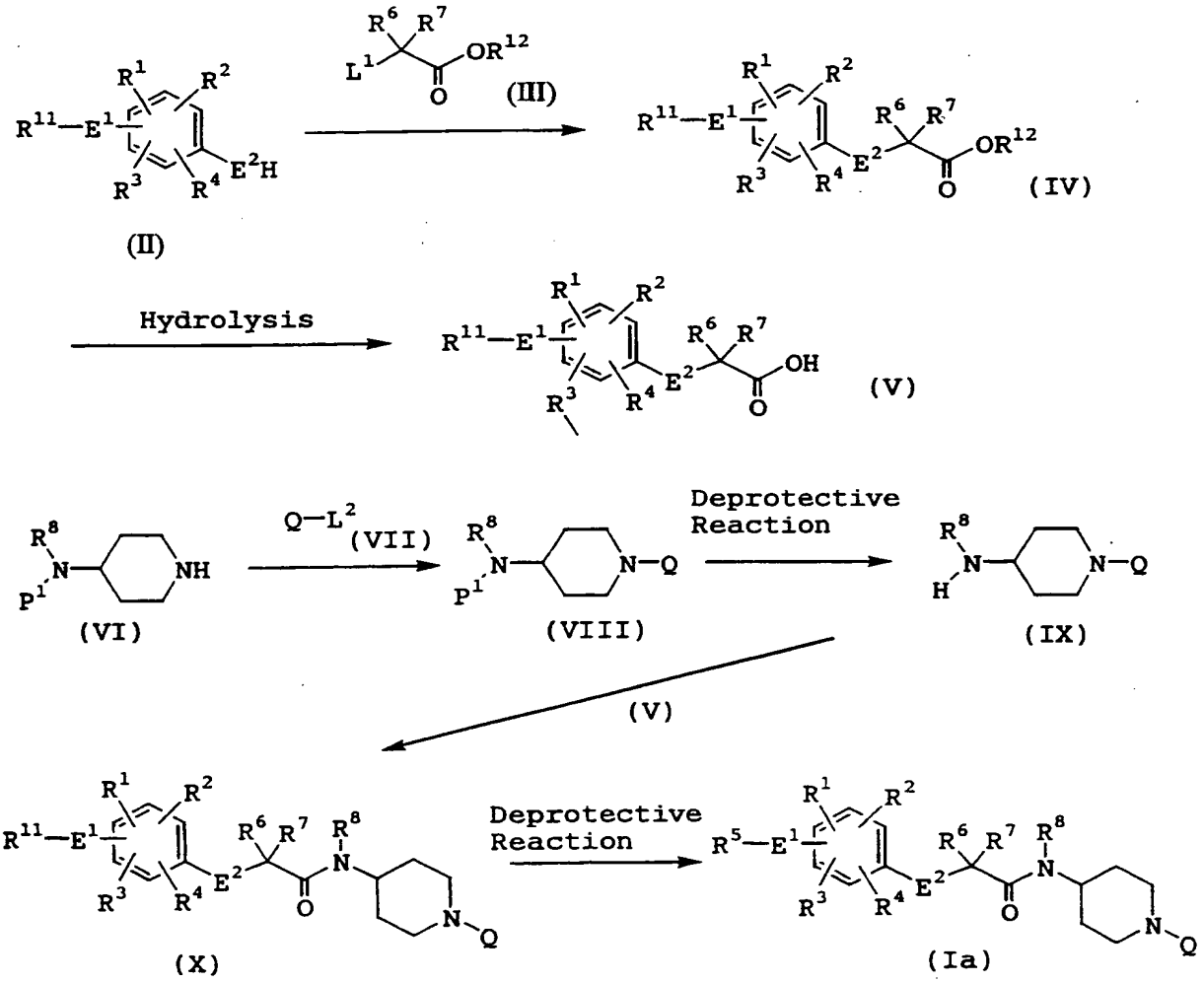
The compound (Ib), the aminophenoxyacetamide derivative of formula (I) in the Claim 2 of the present invention, can be obtained by the following. The amide compound (XII) is obtained by condensation reaction of the carboxylic acid derivative (V'), which is obtained in the Process 1, with compound (XI), and the protecting group of the resultant was removed (Process 2).

The compound (Ib), obtained in the Process 2, can be converted to the compound (Ic) by the reaction with the compound (XIII) (Process 3).

Furthermore, the compound (Id) can be obtained by reacting the compound (Ib) with the compound (XIV) (Process 4).

Each process will be further illustrated by the following reaction scheme.

Process 1:



wherein, R^1 to R^8, E^1 and E^2 have the same definitions as above; Q has the same meaning as defined in claim 1; and R^{11} is alkyl group

which may be substituted, aryl group which may be substituted; aralkyl group which may be substituted; tert-butoxycarbonyl group; ethoxycarbonyl group; acetyl group; benzyloxycarbonyl group; p-methoxybenzyloxycarbonyl group; R^{12} is a straight-chained or branched-chained C_1-C_5 alkyl group; L^1 is leaving group which can easily be replaced with amino, hydroxy and mercapto group; L^2 is leaving group which can be easily replaced with amino, and boric acid; P^1 is tert-butoxycarbonyl group, ethoxycarbonyl group, acetyl group, benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, benzyl group or trifluoroacetyl group.

According to this process 1, the compound (Ia) can be obtained from the known starting compound (II).

Namely, for the first step, the compound (II) is reacted with 1.0 to 1.5 mole equivalent of ester compound (III) in the inert solvent, and if necessary in the presence of the base, under stirring at -20° C to 150° C, preferably at 0° C to 100° C.

The inert solvent to be used in the reaction may be benzene, toluene, tetrahydrofuran, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, acetone, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol, diethyl ether and the like.

The base to be used in the above reaction may be an organic base such as triethylamine, diisopropylethylamine, pyridine and the like, or an inorganic base such as sodium, sodium hydride, potassium, potassium hydride, sodium methoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, sodium bicarbonate, potassium bicarbonate and the like. These organic base and inorganic base may be used in combination, and sodium iodide, potassium iodide or tetrabutylammonium iodide can be added in the reaction mixture.

The substituent "L^1" in the ester derivative (III) may be

the leaving group which can easily be replaced with amino, hydroxy or mercapto group, and examples include halogen atom such as chlorine atom, bromine atom, iodide atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group, 3-nitrobenzenesulfonyloxy group and the like.

The compound (II) and compound (III) to be used in this reaction can be commercially available and known compounds, or can be easily prepared from known compounds by using common methods.

Examples of the compound (II) include 4-(tert-butoxycarbonylamino)phenol, 4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenol, 2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylphenol, 3-(tert-butoxycarbonylamino)-2,4,5,6-tetramethylphenol, 4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenol, 4-(tert-butoxycarbonylamino)-2-chloro-3,5,6-trimethylphenol, 4-(tert-butoxycarbonylamino)-2,3,6-trimethylphenol, 4-(tert-butoxycarbonylamino)-2,3-dimethylphenol, 4-(tert-butoxycarbonylamino)-2,5-dimethylphenol, 2-(tert-butoxycarbonylamino)-4,6-dimethylphenol, 5-(tert-butoxycarbonyl-amino)-2-methoxyphenol, 5-(tert-butoxycarbonylamino)-4-chloro-2-metoxyphenol, 4-(tert-butoxycarbonylamino)-2,6-dichlorophenol, 4-(tert-butoxycarbonylamino)-2,3,4,6-tetramethylaniline, 4-metoxy-2-methylaniline, 4-(tert-butoxycarbonylamino)-2,5-dimethylaniline, 2-(tert-butoxycarbonylamino)-4,5-dimethylaniline, 3-(tert-butoxycarbonylamino)-2,4,6-trimethylaniline, 2-(tert-butoxycarbonylamino)-4,5-dimethylaniline, 4-(tert-butoxycarbonylamino)-2,5-dichloroaniline, 4-(tert-butoxycarbonylamino)-2,6-dichloroaniline, 2-(tert-butoxy carbonylamino)-4,5-dichloroaniline, 4-(tert-butoxycarbonylamino)-2-methoxy-5-methylaniline, 4-(tert-butoxycarbonylamino)-2,5-dimethoxyaniline, 4-(benzyloxycarbonylamino)phenol, 4-(benzyloxycarbonylamino)-2,3,5,6-tetramethylphenol, 2-(benzyloxy-

carbonylamino)-3,4,5,6-tetramethylphenol, 3-(benzyloxycarbonylamino)-2,4,5,6-tetramethylphenol, 4-(benzyloxycarbonylamino)-2,3,5-trimethylphenol, 4-(benzyloxycarbonylamino)-2-chloro-3,5,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3-dimethylphenol, 4-(benzyloxycarbonylamino)-2,5-dimethylphenol, 2-(benzyloxycarbonylamino)-4,6-dimethylphenol, 5-(benzyloxycarbonylamino)-2-methoxyphenol, 5-(benzyloxycarbonylamino)-4-chloro-2-methoxyphenol, 4-(benzyloxycarbonylamino)-2,6-dichlorophenol, 4-(benzyloxycarbonylamino)-2,3,4,6-tetramethylaniline, 4-methoxy-2-methylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethylaniline, 2-(benzyloxycarbonylamino)-4,5-dimethylaniline, 3-(benzyloxycarbonylamino)-2,4,6-trimethylaniline, 2-(benzyloxycarbonylamino)-4,5-dimethylaniline, 4-(benzyloxycarbonylamino)-2,5-dichloroaniline, 4-(benzyloxycarbonylamino)-2,6-dichloroaniline, 2-(benzyloxycarbonylamino)-4,5-dichloroaniline, 4-(benzyloxycarbonylamino)-2-methoxy-5-methylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethoxyaniline and so on.

The ester compound of the formula (III) includes, for example, ethyl bromoacetate, ethyl 2-bromopropionate, ethyl 2-bromo-2-methylpropionate, and so on.

Then, the obtained compound (IV) is hydrogenated to convert into carboxylic acid derivative (V) by the common methods.

The compound (IX) to be used for the condensation reaction with the above-obtained carboxylic acid derivative (V) can be obtained by the following manner.

Namely, for the first step, the amine derivative (VI) is conducted by the condensation reaction with the compound (VII) in the inert solvent, and if necessary in the presence of the base, under stirring at the room temperature to 180°C, to obtain the

compound (VIII).

The inert solvent to be used in the reaction may be benzene, toluene, xylene, diethylaniline, tetrahydrofuran, diethylether, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, methanol, ethanol, propane-2-ol, butyl alcohol and the like.

The base to be used in the above reaction may be an organic base such as triethylamine, diisopropylamine, and the like, or an inorganic base such as sodium hydride, potassium hydride, sodium tert-butoxide, potassium, tert-butoxide, sodium ethoxide, sodium carbonate, sodium bicarbonate, cesium carbonate and the like.

The reaction of the amine compound (VI) with the compound (VII) can also be conducted in the inert solvent such as benzene, toluene, xylene and tetrahydrofuran, and in the presence of palladium catalyst such as tris(dibenzylidene-acetone)dipalladium, diacetoxypalladium, palladium chloride and the like, phosphine coordination compound such as tir-n-butylphosphine, tri-tert-butylphosphine, tri-o-tolylphosphine, BINAP and the like, and the base such as sodium tert-butoxide and c sium carbonate under stirring at 50° C to 150° C.

Furthermore, the reaction of the compound (VII), in which the substitute "L^2" is boronic acid residue, with the amine compound (VI) can be conducted in the inert solvent, and in the presence of the base and 1.0 to 2.0 mole equivalent of copper acetate ($CuOAc_2$), under stirring at the room temperature to 100° C [D. M. T. Chan et al., *Tetrahedron Letters*, 39, 2933 (1998)].

The inert solvent to be used in this reaction may be dichloromethane, chloroform and the like, and the base may be triethylamine, pyridine and the like.

The compound (VI) to be used for the reaction with the compound (VII) is known compound [cf. R. H. Mach et al., *J. Med.*

Chem., 36, 3707 (1993)], or can be easily prepared by the methods described in EP 0184257 A1 [R. A. Stokbroekx, et al.].

Then, the protecting group at nitrogen atom of the compound (VIII) thus obtained is removed to obtain the amine derivative (IX).

This reaction may vary depending on the protecting group on the nitrogen atom of the compound (VIII). For example, the compound (VIII) is treated with acids such as acetic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrochloric acid, sulfuric acid, or nitric acid in an inert solvent such as benzene, toluene, acetonitrile, tetrahydrofuran, dioxane, dichloromethane, chloroform, carbon tetrachloride, water, methanol, ethanol, and the like.

Furthermore, the removal of the protecting group may also be carried out by hydorgenolysis of the compound (VIII) under 1 to 5 atom of hydrogen, in the presence of a catalyst such as palladium-carbon, palladium hydroxide, platinum, or platinum oxide, in an inert solvent such as methanol, ethanol, isopropyl alcohol, ethyl acetate or acetic acid.

Then, the carboxylic acid derivative of the formula (V) is converted into amide derivative (X) by reaction with the compound (IX).

The reaction conditions of this amidation reaction may vary according to the methods described in "*Compendium for Organic Synthesis*" (wiley-Interscience: A Division of John Wiley & Sons Ltd.).

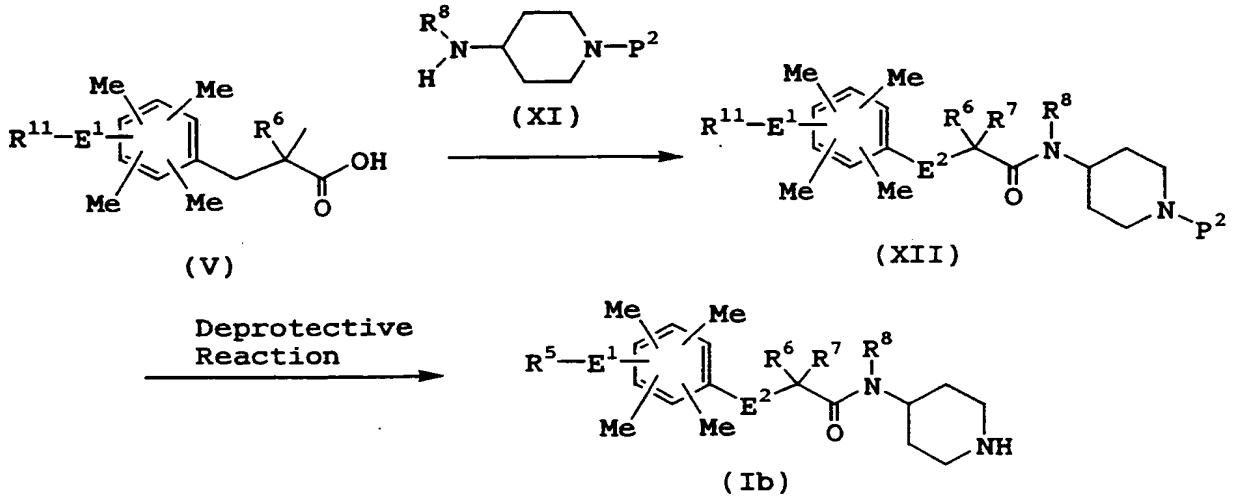
For example, the compound (V) is treated, optionally in the presence of an organic or an inorganic base, with diethyl cyanophosphonate (DEPC), diphenylphosphoryl azide (DPPA), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride or 2-iodo-1-methyl-pyridinium iodide, and then reacted with compound (IX) to obtain the amide

compound (X). Furthermore, the compound (V) is converted into the activated ester compound such as acid halide, symmetric acid anhydride, or mixture acid anhydride, and then, reacted with the compound (IX) to obtain the amide compound (X).

The compound (X) thus obtained is converted into the aminophenoxyacetamide derivatives of the formula (Ia), the compound of the present invention, by the removal reaction of the protecting group on the nitrogen atom of the amide compound (X).

Although each compounds obtained in the above process 1 may be used for the next reaction without further purification, it can also be used after further purification if necessary in conventional manner such as recrystallization or column chromatography and so on.

Process 2:



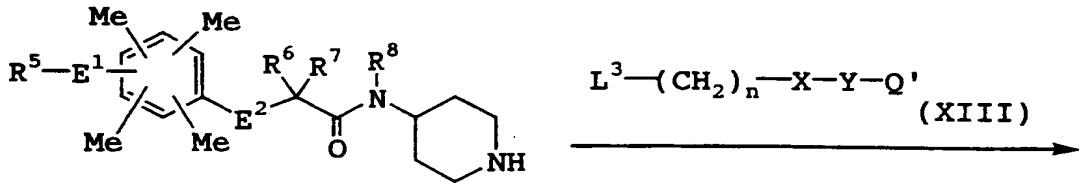
wherein, R^5 to R^8 and R^{11} have the same definitions as above, E^1 and E^2 have the same meanings as defined in claim 2, and P^2 is tert-butoxycarbonyl group, ethoxycarbonyl group, acetyl group, benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, benzyl group or trifluoroacetyl group.

According to this process 2, the aminophenoxyacetamide derivative of the formula (Ib) can be synthesized from the compound (V') [wherein, R^1 to R^4 are methyl groups, E^1 is oxygen atom and E^2 is $-NR^9$; or E^1 is $-NR^{10}$ and E^2 is oxygen atom] obtained in the process 1 mentioned above.

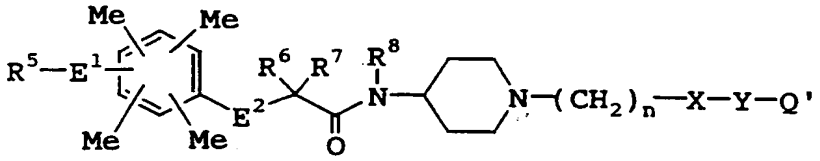
Namely, the compound (V') [wherein, R^1 to R^4 are methyl groups, E^1 is oxygen atom and E^2 is $-NR^9$; or E^1 is $-NR^{10}$ and E^2 is oxygen atom] is reacted with the compound (XI) to obtain the amide compound (XII), and then, the protecting group of the resultant compound (XII) is removed off to give the aminophenoxyacetamide derivative (Ib).

This reaction may be carried out by the same manner as described in the Process 1.

Process 3:



(Ib)



(Ic)

wherein, R^5 to R^8 and have the same definitions as above, n, X, Y, Q', E^1 and E^2 have the same meanings as defined in claim 2.

According to this process 3, the aminophenoxyacetamide derivative of the formula (Ic) can be obtained from the compound (Ib) by reacting with the compound (XIII).

Namely, the compound (Ib) is reacted with 1.0 to 1.5 mole

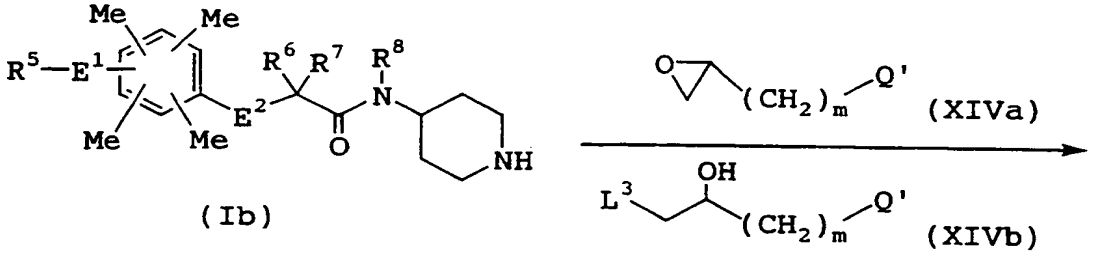
equivalent of the compound (XIII) in the inert solvent such as benzene, toluene, tetrahydrofuran, dioxan, dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone, ether, dichloromethane, chloroform and carbon tetrachloride in the presence of the base, at -50° C to 120° C, preferably at -20° C to 80° C.

The base to be used in the reaction may be an organic base such as triethylamine, diisopropylethylamine, pyridine and the like, or an inorganic base such as sodium, sodium hydride, potassium, potassium hydride, sodium ethoxide, sodium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, sodium bicarbonate, potassium bicarbonate and the like. Sodium iodide, potassium iodide or tetrabutylammonium iodide can be added in the reaction mixture.

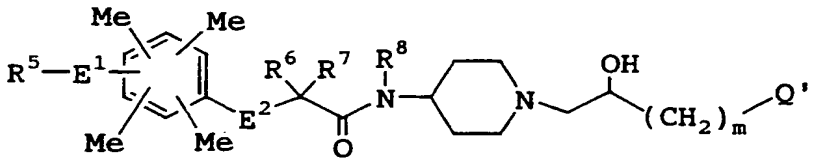
The substituent "L^3" in the compound (XIII) is the leaving group, which can easily be replaced by amino group, and examples include halogen atom such as chlorine atom, bromine atom, iodine atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group and the like.

In this process 3, the aminophenoxyacetamide derivative of the formula (Ic) can be produced as well.

Process 4:



(Ib) (XIVa) (XIVb)



(Id)

wherein, R^5 to R^8 and L^3 have the same definitions as previously mentioned, Q', E^1 and E^2 are the same meanings as defined in the claim 2, and m is integer 0 to 3.

According to this process 4, the aminophenoxyacetamide derivative of the formula (Id) of the present invention can be obtained from the reaction of the compound (Ib), obtained in the process 2 mentioned above, with the compound (XIVa) or the compound (XIVb).

For example, the compound (Ib) is reacted with 0.9 to 1.5 moles equivalent of the compound (XIVa) or (XIVb) in an inert solvent at from room temperature to about 200 °C, preferably at about 50°C to about 150°C, to produce the aminophenoxyacetamide of the formula (Id).

The inert solvent to be used in the reaction may be benzene, toluene, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol and the like.

Examples of the compound (XIVa) include epibromohydrin, epichlorohydrin, (R)-epichlorohydrin, (S)-epichlorohydrin and the

like, and examples of the compound (XIVb) include glycidyl tosylate, (R)-glycidyl tosylate, (S)-glycidyl tosylate, (R)-glycidyl 3-nitro-benzensulfonate, (S)-glycidyl 3-nitrobenzesulfonate, (R)-glycidyl 4-nitro-benzoate, (S)-glycidyl 4-nitrobenzoate, gylcidyltrimethylammonium chloride and the like.

In this process 4, the aminophenoxyacetamide derivative of the formula (Id) can be produced as well.

The aminophenoxyacetamide derivatives of the formula (I) thus obtained may be isolated and purified in conventional manner, such as recrystallization, column chromatography and the like.

Further, each isomers contained in the compounds of the formula (I) of the present invention can be obtained by resolution of the isomeric mixture of these compounds by the conventional methods, such as recrystallization, column chromatography, HPLC, and the like, or by using optically active reagents.

The aminophenoxyacetamide derivatives of the present invention represented by the formula (I) may be used in the form of free bases or suitable pharmaceutically acceptable acid addition salts thereof. The pharmaceutically acceptable salts can be obtained by treating the compound (I) with an inorganic acid or an organic acid in suitable organic solvent such as ether, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, methanol, isopropanol, ethanol and the like.

Examples of the inorganic acid include hydrochloric acid, sulfuric acid, hydrobromic acid, phosphoric acid, periodic acid and the like. Further, examples of the organic acid include formic acid, acetic acid, butyric acid, oxalic acid, malonic acid, propionic acid, valeric acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, benzoic acid, p-

toluenesulfonic acid, methanesulfonic acid and the like.

The aminophenoxyacetamide derivatives of the present invention represented by the formula (I) or pharmaceutically acceptable salts thereof shows low toxicity and may be administered per se. However, it may be converted in the form of pharmaceutically acceptable composition with the conventional pharmaceutically acceptable carriers for improvement or treatment of various kinds of diseases due to cerebral functional or organic disorder.

The dosage forms may include oral formulations such as capsules, tablets or parenteral formulations such as injection solution containing the compound of the formula (I) *per se*, or using the conventional excipients. For example, the capsules can be prepared by mixing the compound of the formula (I) in powder form with a suitable excipient such as lactose, starch or derivatives thereof or cellulose derivatives, and then filled in gelatin capsules.

Also, the tablets can be prepared by mixing the active ingredients with the above-mentioned excipients, binders such as sodium carboxymethylcellulose, alginic acid or gum arabic and water, then if necessary, making the resultant mixture into granules. Then, it may be further mixed with lubricant such as talc or stearic acid, and compressed into tablet by mean of common tableting machine.

Injectable formulations for parenteral route also can be prepared by dissolving the compound of the formula (I) or salts thereof in sterile distilled solution or sterile physiological saline solution with solution adjuvant, and filling it into ample. A stabilizer or buffer can be used in the injectable solution, and the injectable formulation may be administered intravenously or by dripping.

In administration of the compound of the formula (I), which possesses neuroprotective effect by induction of CalbindinD-28k, one of Ca^{2+}-bindind proteins, the therapeutically effective dosage for improving cerebral functional and organic disorders is not particularly limited and may vary depending on the various kinds of factors. These factors may be the patient's condition, the severity of the disease, age, existence of a complication, administration route, formulation, as well as number of times for administration.

A usual recommended daily dose for oral administration is within the range of 0.1-1,000 mg/day/person, preferably 1-500 mg/day/person, while a usual recommended daily dose for parenteral administration is within the range of 1/100 to 1/2 based on dose of the oral administration. These doses also may vary depending on age, as well as the patient's condition.

Examples:

The present invention is illustrated in more detail by way of the following examples, but it is to be noted that the present invention is not limited by these Examples in any way.

The compound numbers in the following examples are identical to those of the Table's mentioned later.

Example 1: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (1)

A solution of 457 mg of 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenoxy]acetic acid, 363 mg of 1-(tert-butoxycarbonylamino)-4-methylaminopiperidine, 2.16 g of 25% propane phosphonic acid anhydride [Japanese Patent Kokai Showa 55-100346] in ethyl acetate solution and 985 µl of triethylamine in 5 ml of dichloromethane was stirred over night under room temperature. After the reaction, saturated sodium hydrogen carbonate aqueous

solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The extract was washed with saline, dried and concentrated under reduced pressure to give the residue. The obtained residue was dissolved in 8 ml of dichloromethane, and to this solution was added 2 ml of trifluoroacetic acid under ice-cooling, then the mixture was stirred for 1 hour at the room temperature. After removal of the solvent, the resultant residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.) column chromatography (dichloromethane : methanol = 30:1) to give 192 mg (42%) of the above-mentioned compound (1).

Example 2: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-(4-piperidinyl)propanamide (2)

The title compound (2) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenoxy]propionic acid and 1-(tert-butoxycarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

Example 3: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-2-methyl-N-methyl-N-(4-piperidinyl)propanamide (3)

The title compound (3) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenoxy]-2-methyl propionic acid and 1-(tert-butoxycarbonylamino)-4-methylamino-piperidine by the same manner as the Example 1.

Example 4: 2-(2-Amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (4)

The title compound (4) was obtained from 2-[2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylphenoxy]acetic acid and 1-(tert-butoxylcarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

Example 5: 2-(3-Amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (5)

The title compound (5) was obtained from 2-[3-(tert-butoxycarbonylamino)-2,4,5,6-tetramethylphenoxy]acetic acid and 1-(tert-butoxycarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

Example 6: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-(1-phenethyl-4-piperidinyl)acetamide (6)

To a mixture solution of 99 mg of the compound (1) obtained in the Example 1 and 42.3 μl of phenethyl bromide in 2 ml of acetonitrile was added 65 μl of triethylamine, and the mixture was stirred for 5 hours at 60°C. After the reaction, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with saline, dried and concentrated under reduced pressure to give the residue. The obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.) column chromatography (dichloromethane : ther = 1:1) to give 86 mg (65%) of the above-mentioned compound (6).

Example 7: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylacetamide (7)

The title compound (7) was obtained from the compound (1) obtained in the Example 1 and N-phenyl-2-bromoacetamide by the same manner as the Example 6.

Example 8: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-(1-benzoyl-4-piperidinyl)-N-methylacetamide (8)

The title compound (8) was obtained from the compound (1)

obtained in the Example 1 and benzoyl chloride by the same manner as the Example 6.

Example 9: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-(1-butyl-4-piperidinyl)-N-methylacetamide (9)

The title compound (9) was obtained from the compound (1) obtained in the Example 1 and butyl bromide by the same manner as the Example 6.

Example 10: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-phenyl-2-oxoethyl)-4-piperidinyl]-N-methylacetamide (10)

The title compound (10) was obtained from the compound (1) obtained in the Example 1 and phenacyl bromide by the same manner as the Example 6.

Example 11: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylacetamide (11)

To a mixture solution of the compound (10) obtained in the Example 10 in methanol was added 1.0 equivalent of sodium borohydride at 0°C, and the mixture was stirred for 1.5 hours at the room temperature. After the reaction, the solvent was removed under reduced pressure, and the resulting residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.) column chromatography (dichloromethane : methanol = 20:1) to give the above-mentioned compound (11) in the yield of 58%.

Example 12: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-(1-cyclopropylmethyl-4-piperidinyl)-N-methylacetamide (12)

The title compound (12) was obtained from the compound (1) btained in the Example 1 and cyclopropylmethyl bromide by the same manner as the Example 6.

Example 13: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]acetamide (13)

The title compound (13) was obtained from the compound (1) obtained in the Example 1 and *trans*-2-phenyl-1-cyclopropylmethyl bromide by the same manner as the Example 6.

Example 14: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]acetamide (14)

The title compound (14) was obtained from the compound (1) obtained in the Example 1 and 2-phenoxyethyl bromide by the same manner as the Example 6.

Example 15: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(N-methylanilino)-2-oxoethyl]-4-piperidinyl}acetamide (15)

The title compound (15) was obtained from the compound (1) obtained in the Example 1 and N-methyl-N-phenyl-2-bromoacetamide by the same manner as the Example 6.

Example 16: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}acetamide (16)

The title compound (16) was obtained from the compound (1) obtained in the Example 1 and N-(2-bromoethyl)morpholine hydrochloride by the same manner as the Example 6.

Example 17: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-{1-[2-(2-hydroxy-2-phenylethoxy)ethyl]-4-piperidinyl}-N-methylacetamide (17)

The title compound (17) was obtained from the compound (1) obtained in the Example 1 and 2-(chloroethoxy)-1-phenylethanol by the same manner as the Example 6.

Example 18: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-[1-(4-cyanobenzyl)-4-piperidinyl]-N-methylacetamide (18)

The title compound (18) was obtained from the compound (1) obtained in the Example 1 and 4-cyanobenzyl bromide by the same manner as the Example 6.

Example 19: 4-({4-[[(4-Amino-2,3,5,6-tetramethylphenoxy)acetyl]-(methyl)amino]-1-piperidinyl}methyl)bezamide (19)

To a mixture solution of 82 mg of the compound (18) obtained in the Example 18 in methanol were added 58 µl of 30% hydrogen peroxide aqueous solution and 150 µl of 3N-sodium hydroxide aqueous solution under ice-cooling, and the reaction mixture was stirred for 6 hours at the room the temperature. After the reaction, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture, and extracted with dichloromethane. The organic layer was washed with saturated saline, dried and the solvent was removed under reduced pressure. The resulting residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.) column chromatography (dichloromethane : methanol = 10:1) to give 66 mg (77%) of the above-mentioned compound (19).

Example 20: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylthio)ethyl]-4-piperidinyl}acetamide (20)

The title compound (20) was obtained from the compound (1) obtained in the Example 1 and 2-(chloroethyl)phenyl sulfide by the same manner as the Example 6.

Example 21: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-propynyl)-4-piperidinyl]acetamide (21)

The title compound (21) was obtained from the compound (1) obtained in the Example 1 and propargyl bromide by the same manner as the Example 6.

Example 22: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-methyl-2-phenylethyl)-4-piperidinyl]acetamide (22)

The title compound (22) was obtained from the compound (1) obtained in the Example 1 and 2-bromo-1-phenylpropane by the same manner as the Example 6.

Example 23: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-(1-cyclopropylmethyl-4-piperidinyl)-N-methylpropanamide (23)

The title compound (23) was obtained from the compound (2) obtained in the Example 2 and cyclopropylmethyl bromide by the same manner as the Example 6.

Example 24: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-(1-butyl-4-piperidinyl)-N-methylpropanamide (24)

The title compound (24) was obtained from the compound (2) obtained in the Example 2 and 1-bromobutane by the same manner as the Example 6.

Example 25: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methy-N-{1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}propanamide (25)

The title compound (25) was obtained from the compound (2) obtained in the Example 2 and N-(2-bromoethyl)morpholine hydrochloride by the same manner as the Example 6.

Example 26: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]propanamide (26)

The title compound (26) was obtained from the compound (2) obtained in the Example 2 and *trans*-2-phenyl-1-cyclopropylmethyl bromid by the same manner as the Example 6.

Example 27: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-

[2-(N-methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide (27)

The title compound (27) was obtained from the compound (2) obtained in the Example 2 and N-methyl-N-phenyl-2-bromoacetamide by the same manner as the Example 6.

Example 28: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (28)

The title compound (28) was obtained from the compound (3) obtained in the Example 3 and phenethyl bromide by the same manner as the Example 6.

Example 29: 2-(2-Amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenylethyl)-4-piperidinyl]acetamide (29)

The title compound (29) was obtained from the compound (4) obtained in the Example 4 and phenethyl bromide by the same manner as the Example 6.

Example 30: 2-(2-Amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-phenyl-2-oxoethyl)-4-piperidinyl]-N-methylacetamide (30)

The title compound (30) was obtained from the compound (4) obtained in the Example 4 and phenacyl bromide by the same manner as the Example 6.

Example 31: 2-(2-Amino-3,4,5,6-tetramethylanilino)-N-methyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]acetamide (31)

The title compound (31) was obtained from 2-[2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylanilino]acetic acid and 1-(4-phenoxyphenyl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 32: 2-(2-Amino-3,4,5,6-tetramethylanilino)-N-{1-[4-(4-fluorobenzyl)phenyl]-4-piperidinyl}-N-methylacetamide (32)

The title compound (32) was obtained from 2-[2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylanilino]acetic acid and 1-[4-(4-fluorobenzyl)phenyl]-4-methyaminopiperidine by the same manner as the Example 1.

Example 33: 2-(3-Amino-2,4,5,6-tetramethylphenoxy)-N-(1-benzoyl-4-piperidinyl)-N-methylacetamide (33)

The title compound (33) was obtained from the compound (5) obtained in the Example 5 and benzoyl chloride by the same manner as the Example 6.

Example 34: 2-(3-Amino-2,4,5,6-tetramethylphenoxy)-N-[1-(4-cyanobenzyl)-4-piperidinyl]-N-methylacetamide (34)

The title compound (34) was obtained from the compound (5) obtained in the Example 5 and 4-cyanobenzyl bromide by the same manner as the Example 6.

Example 35: 2-(3-Amino-2,4,5,6-tetramethylphenoxy)-N-methy-N-[1-(2-phenylethyl)-4-piperidinyl]acetamide (35)

The title compound (35) was obtained from the compound (5) obtained in the Example 5 and phenethyl bromide by the same manner as the Example 6.

Example 36: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(4-fluorophenyl)-4-piperidinyl]-N-methylacetamide (36)

The title compound (36) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]acetic acid and 1-(4-fluorophenyl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 37: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylacetamide (37)

The title compound (37) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]acetic acid and 1-(1,3-benzothiazol-2-yl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 38: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(4-fluorophenyl)-4-piperidinyl]-N-methylacetamide (38)

The title compound (38) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]acetic acid and 1-(4-fluorophenyl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 39: 2-(3-Amino-2,4,6-trimethylanilino)-N-[1-(4-fluorophenyl)-4-piperidinyl]-N-methylacetamide (39)

The title compound (39) was obtained from 2-[3-(tert-butoxycarbonylamino)-2,4,6-trimethylanilino]acetic acid and 1-(4-fluorophenyl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 40: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanamide (40)

The title compound (40) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]propionic acid and 1-(4-phenoxyphenyl)-4-methyaminopiperidine by the same manner as the Example 1.

Example 41: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-(1-[1,1'-biphenyl]-4-yl-4-piperidinyl)-N-methylpropanamide (41)

The title compound (41) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]propionic acid and 1-[1,1'-biphenyl]-4-yl-N-methyl-4-piperidine amine by the same manner as the Example 1.

The physiochemical datum of the compounds obtained by the above-mentioned examples is summarized in the following tables 1 to 7.

Table 1:

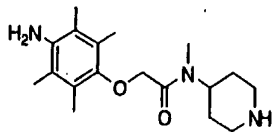
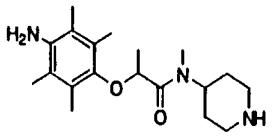
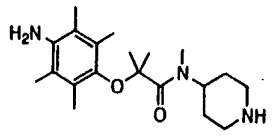
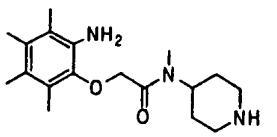
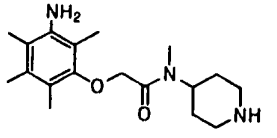
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
1		white powder	($CHCl_3$) 2950, 2399, 1734, 1652, 1558, 1472, 1418, 1319, 1083	1.53-1.85(4H, m), 2.08(3H, s), 2.09(3H, s), 2.23(3H, s), 2.24(3H, s), 2.63(1H, m), 2.76(1H, m), 2.88&2.92(3H, each s), 3.15(2H, m), 3.48(2H, brs), 3.73&4.63(1H, each m), 4.31&4.36(2H, each s)
2		white powder	3378, 2938, 1638 1472, 1416, 1370 1286, 1257, 1077	1.42 & 1.43 (3H, d, J = 6.5 Hz), 1.54-1.72 (4H, m), 2.08 (6H, s), 2.19 (6H, s), 2.35 & 2.53 (1H, each m), 2.74 (1H, m), 2.80 & 2.84 (3H, each s), 3.08 (2H, m), 3.44 (2H, brs), 3.80 (0.5H, m), 4.58 (1.5H, m)
3		pale yellow powder	($CHCl_3$) 2401, 1624, 1474 1412, 1384, 1256 1145, 1076	1.41 (6H, s), 1.61-1.80 (4H, m), 2.04 & 2.07 & 2.08 & 2.11 & 2.13 (12H, each s), 2.65 (1H, m), 2.75 (1H, m), 2.89 & 3.34 (3H, each s), 3.14 (2H, m), 3.45 (2H, brs), 4.60 & 4.90 (1H, m)
4		white powder	($CHCl_3$) 2401, 1654, 1474 1238, 1077, 1044 928	1.49-1.73 (4H, m), 2.10 (3H, s), 2.13 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 2.53-2.81(2H, m), 2.76&2.91 (3H, each s), 3.14 (2H, m), 3.40&4.61 (1H, m), 3.96-4.33 (2H, brs), 4.47&4.51 (2H, each s)
5		yellow oil	($CHCl_3$) 2932, 2402, 1654 1451, 1320, 1122 1084, 1050	1.61-1.81 (4H, m), 2.09 & 2.13 & 2.18 & 2.22 (12H, each s), 2.63 (2H, m), 2.77 (2H, m), 2.88 & 2.92 (3H, each s), 3.16 & 3.18 (2H, each m), 3.52 (2H, brs), 3.72 & 4.63 (1H, each m), 4.34 & 4.38 (2H, each s)

Table 2:

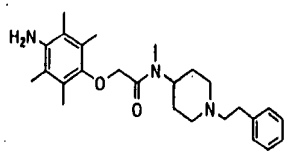
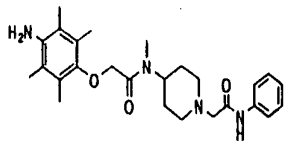
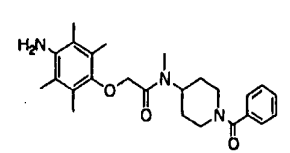
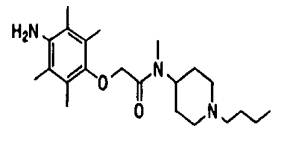
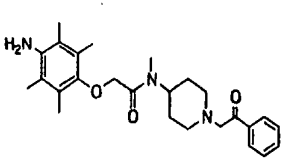
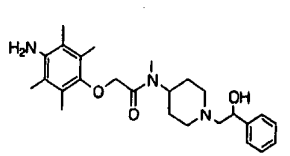
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
6		white powder (2·HCl salt) (Et_2O/MeOH) 261-263°C	(2·HCl salt) 3432, 2926, 2345, 1646, 1534, 1478, 1455, 1304, 1248, 1098	1.56-2.29(6H, m), 2.09(6H, s), 2.23(3H, s), 2.24(3H, s), 2.61(2H, m) 2.75-2.85(2H, m), 2.88&2.92(3H, each s), 3.09(2H, m), 3.47(2H, brs 3.69&4.58(1H, each m), 4.32&4.35(2H, each s), 7.20(3H, m), 7.24-7.33(2H, m)
7		white powder (2·HCl salt) (Et_2O/MeOH) 196-200°C	(2·HCl salt) 3425, 2950, 1692, 1636, 1556, 1498, 1447, 1314, 1248, 1097	1.68-2.04(4H, m), 2.09(6H, s), 2.23(6H, s), 2.29-2.55(2H, m), 2.94&2.96(3H, each s), 3.00(2H, m), 3.14&3.16(2H, each s), 3.49(2H, brs), 3.81&4.57(1H, each m), 4.33&4.36(2H, each s), 7.12(1H, m), 7.35(2H, m), 7.57(2H, d), 8.96&9.06(1H, each brs)
8		white powder (HCl salt) (Et_2O/MeOH) 202-203°C	(2·HCl salt) 3457, 2922, 2586 1633, 1530, 1448, 1318, 1250, 1108 1043, 713	1.78 (4H, m), 2.08 (6H, s), 2.22 (6H, s), 2.89 (3H, s), 2.89-3.06 (2H, brs), 3.47 (2H, brs), 3.87 (1H, brs), 4.06 & 4.79 (1H, each m), 4.32 & 4.37 (2H, each s), 4.82 (1H, brs), 7.41 (5H, m)
9		white powder (2·HCl salt) (Et_2O/MeOH) 229-230°C	(2·HCl salt) 3428, 2956, 1648, 1522, 1463, 1419, 1309, 1248, 1106, 1091, 1046	0.92 (3H, m), 1.33 &1.45 (4H, each m), 1.74-2.32 (8H, m), 2.08 (6H, s), 2.22 (6H, s), 2.88 & 2.90 (3H, each s), 2.99 & 3.01 (2H, each m), 3.46 (2H, brs), 3.68 & 4.11 & 4.54 (1H, each m), 4.31 & 4.34 (2H, each s),
10		white powder (2·HCl salt) (Et_2O/MeOH) 201-203°C	(2·HCl salt) 3417, 2938, 1694, 1646, 1598, 1450, 1417, 1247, 1101,	1.69 (2H, m), 1.89 (1H, m), 2.08 (6H, s), 2.22 (6H, s), 2.30 (1H, m), 2.89 (3H, s), 2.91 & 3.09 (4H, each m), 3.74 & 4.59 & 4.81 (1H, each m), 3.82 & 3.85 (2H, each s), 4.32 & 4.35 (2H, each s), 7.46 & 7.57 (3H, each m), 7.97 (2H, m)
11		white powder (2·HCl salt) (Et_2O/MeOH) 229-230°C	(2·HCl salt) 3375, 2945, 1646, 1460, 1248, 1100, 700	1.73-2.56 (8H, m), 2.09 (6H, s), 2.23 (6H, s), 2.90 & 3.25 (2H, each m), 2.90 & 2.92 (3H, each s), 3.47 (2H, brs), 3.76 & 4.58 (1H, each m), 4.33 & 4.35 (2H, each s), 4.71 & 4.73 (1H, each m), 7.36 (5H, m)

Table 3:

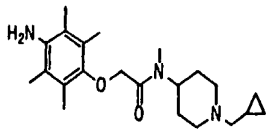
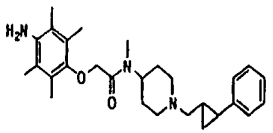
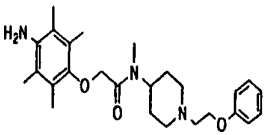
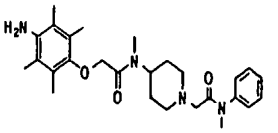
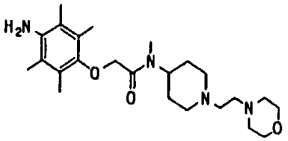
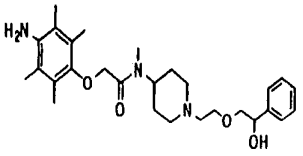
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
12		white powder (2·HCl salt) (Et_2O/MeOH) 223-225°C	(2·HCl salt) 3425, 2932, 1648, 1460, 1414, 1306, 1248, 1095, 1032,	0.11 (2H, m), 0.41 (2H, m), 0.75 & 0.95 (1H, each m), 1.65-2.18 (8H, m), 1.99 (6H, s), 2.10 & 2.13 (6H, each s), 2.78 & 2.81 (3H, each s), 3.05 (2H, m), 3.37 (2H, brs), 3.58 & 4.44 (1H, each m), 4.21 & 4.24 & 4.27 (2H, each s)
13		white powder (2·HCl salt) (Et_2O/MeOH) 216-217°C	(2·HCl salt) 3431, 2941, 1637, 1498, 1460, 1417, 1248, 1096, 1032,	0.82 (1H, m), 0.97 (1H, m), 1.23 (1H, m), 1.66-2.22 (7H, m), 2.08 (6H, s), 2.22 (6H, s), 2.37 (1H, m), 2.53 (1H, m), 2.87 & 2.90 (3H, each s), 3.12 (2H, m), 3.46 (2H, brs), 3.67 & 4.54 (1H, each m), 4.31 & 4.33 (2H, each s), 7.04 (2H, m), 7.14 (1H, m), 7.25 (2H, m)
14		white powder (2·HCl salt) (Et_2O/MeOH) 216-219°C	(2·HCl salt) 3417, 2950, 1638, 1598, 1494, 1413, 1305, 1246, 1099, 1044, 756	1.61-2.38 (6H, m), 2.09 (6H, s), 2.22 (6H, s), 2.82 (2H, m), 2.88 & 2.91 (3H, each s), 3.08 (2H, m), 3.46 (2H, brs), 3.70 & 4.56 (1H, each m), 4.09 (2H, m), 4.31 & 4.34 (2H, each s), 6.90 (3H, m), 7.28 (2H, m)
15		white powder (2·HCl salt) (Et_2O/MeOH) 210-212°C	(2·HCl salt) 3414, 2938, 1663, 1495, 1452, 1368, 1248, 1098, 703	1.79-2.20 (6H, m), 2.07 (6H, s), 2.17 & 2.21 (6H, each s), 2.84 & 2.88 (3H, each s), 2.92 (4H, m), 3.27 (3H, s), 3.47 (2H, m), 3.57 & 4.47 (1H, m), 4.29 & 4.30 (2H, each s), 7.18 (2H, d = 7.3 Hz, J = Hz), 7.36-7.45 (3H, m)
16		white powder (3·HCl salt) (Et_2O/MeOH) 290-293°C	(3·HCl salt) 3442, 2945, 2402, 1668, 1452, 1306, 1294, 1248, 1121, 1102, 1060, 876	1.75-2.23 (6H, m), 2.09 (6H, s), 2.22 (6H, s), 2.50 (8H, m), 2.87 & 2.90 (3H, each s), 3.01 (2H, m), 3.47 (2H, m), 3.47 & 4.54 (1H, each m), 3.71 (4H, m), 4.30 & 4.34 (2H, each s)
17		white powder (2·HCl salt) (Et_2O/MeOH) 228-231°C	(2·HCl salt) 3427, 2950, 1651, 1452, 1415, 1306, 1248, 1124, 1101, 1045, 700	1.67-2.24 (6H, m), 2.09 (6H, s), 2.22 & 2.23 (6H, each s), 2.61 (2H, m), 2.79 (2H, m), 2.89 & 2.92 (3H, each m), 3.08 (2H, m), 3.43 (2H, m), 3.47 (2H, brs), 3.70 & 4.57 (1H, each m), 3.75 (2H, m), 4.32 & 4.35 (2H, each s), 4.87 (1H, m), 7.23 (5H, m)

Table 4:

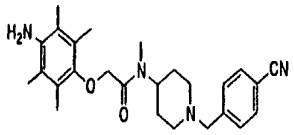
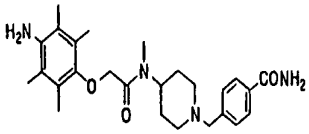
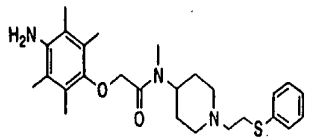
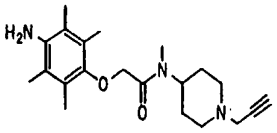
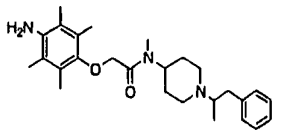
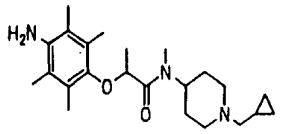
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
18		white powder (2·HCl salt) (Et_2O/MeOH) 251-253°C	(2·HCl salt) 3416, 2918, 2487, 1658, 1631, 1461, 1305, 1248, 1116, 1097	1.66-2.22 (6H, m), 2.08 (6H, s), 2.22 (6H, s), 2.89 & 2.92 (3H, each s), 2.91 (2H, m), 3.47 (2H, brs), 3.55 (2H, s), 3.70 & 4.55 (1H, each m), 4.31 & 4.34 (2H, each s), 7.44(2H, m), 7.60 (2H, m),
19		white powder (2·HCl salt) (Et_2O/MeOH) 226-229°C	(2·HCl salt) 3404, 2940, 1667, 1462, 1421, 1248, 1097	1.65-2.22 (6H, m), 2.08 (6H, s), 2.21 (6H, s), 2.88 & 2.91 (3H, each s), 2.93 (2H, m), 3.46 (2H, brs), 3.53 (2H, s), 3.66 & 4.54 (1H, each m), 4.31 & 4.33 (2H, each s), 4.39 (2H, m), 4.77 (2H, m), 5.74 & 6.12 (2H, brs)
20		white powder (2·HCl salt) (Et_2O/MeOH) 231-233°C	(2·HCl salt) 3427, 2936, 1640, 1459, 1419, 1308, 1247, 1096, 1026, 746, 693	1.67-2.22 (6H, m), 2.08 (6H, s), 2.22 (6H, s), 2.63 (2H, m), 2.87 & 2.90 (3H, each s), 3.03-3.07 (4H, m), 3.67 & 4.53 (1H, each m), 4.11 & 4.13 (2H, each s), 7.18 (1H, m), 7.27 (2H, m), 7.34 (2H, m)
21		white powder (2·HCl salt) (Et_2O/MeOH) 172-174°C	(2·HCl salt) 3406, 2926, 2565 1638, 1459, 1420 1249, 1099	1.65-2.43 (7H, m), 2.09&2.22&2.24&2.26 (12H, each s), 2.88&2.91(3H, each s), 2.97 (2H, m), 3.31 (2H, s), 3.47 (2H, brs), 3.68&4.56 (1H, m), 4.31&4.35 (2H, each s)
22		white powder (2·HCl salt) (Et_2O/MeOH) 212-214°C	(2·HCl salt) 3411, 2936, 1638 1454, 1420, 1249 1098, 1028	0.94 (3H, t), 1.46-2.26 (4H ,m), 2.09&2.23&2.24 (12H, each s), 2.30-2.55 (2H, m), 2.80-3.03 (4H, m), 2.89&2.92 (3H, each s), 3.47 (3H, m), 3.63&4.54(1H, m), 4.32&4.35 (2H, each s), 7.13-7.33 (5H, m)
23		white powder (2·HCl salt) (Et_2O/MeOH) 220-221°C	(2·HCl salt) 3408, 2939, 2592, 1657, 1463, 1415, 1251, 1107, 1079, 1024	0.01 & 0.43 (4H, each m), 0.76 (1H, m), 1.34 & 1.35 (3H, d, J = 6.2 Hz), 1.50-1.83 (6H, m), 1.99 (6H, s), 2.06-2.23 (2H, m), 2.11 (6H, s), 2.72 & 2.76 (3H, each s), 3.02 (2H, m), 3.36 (2H, brs), 3.60 & 4.43 (1H, each m), 4.47 (1H, m)

Table 5:

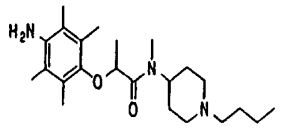
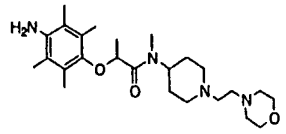
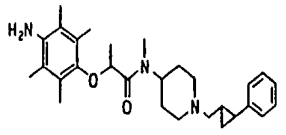
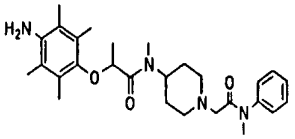
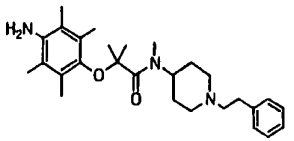
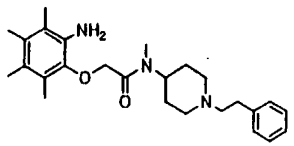
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
24		white powder (2·HCl salt) (Et_2O/MeOH) 228-231°C	(2·HCl salt) 3428, 2931, 1630, 1464, 1374, 1249, 1080, 1024	(2·HCl salt) : CD_3OD 1.02 (3H, m), 1.42 (3H, m), 1.46 (2H, m), 1.71-1.97 (4H, m), 2.19 (2H, m), 2.24 (6H, s), 2.29 (6H, s), 2.87 (3H, s), 3.06 (4H, m), 3.66 (2H, m), 4.12 & 4.60 (1H, each m), 4.79 (1H, m)
25		white powder (3·HCl salt) (Et_2O/MeOH) 266-268°C	(3·HCl salt) 3417, 2942, 2537, 1630, 1454, 1417, 1249, 1101	1.43 (3H, m), 1.54-2.19 (6H, m), 2.07 (6H, s), 2.19 (6H, s), 2.46 & 2.52 (8H, each m), 2.98 (2H, m), 3.45 (2H, brs), 3.71 (4H, m), 3.71 & 4.52 (1H, each m), 4.55 (1H, m)
26		white powder (2·HCl salt) (Et_2O/MeOH) 195-197°C	(2·HCl salt) 3430, 2938, 1636, 1499, 1463, 1414, 1249, 1096, 700	0.81 (1H, m), 0.96 (1H, m), 1.22 (1H, m), 1.43 (3H, m), 1.55-2.39 (8H, m), 2.07 (6H, s), 2.16 & 2.18 (6H, each s), 2.52 (1H, m), 2.78 & 2.83 (3H, each s), 3.06 (2H, m), 3.44 (2H, brs), 3.71 & 4.53 (1H, each m), 4.54 (1H, m), 7.03 (2H, m), 7.23 (1H, m), 7.26 (2H, m)
27		white powder (2·HCl salt) (Et_2O/MeOH) 205-208°C	(2·HCl salt) 3436, 2938, 1653, 1496, 1462, 1414, 1368, 1248, 1071, 700	1.40 (3H, d, J = 6.5Hz), 1.41-2.17 (6H, m), 2.08 & 2.17 & 2.21(12H, each s), 2.84 & 2.88 (3H, each s), 2.92 (4H, m), 3.28 (3H, s), 3.46 (2H, brs), 3.59 & 4.45 (1H, each m), 4.54 (1H, m), 7.18 (2H, d, J = 7.6 Hz), 7.31-7.44 (3H, m),
28		white powder (2·HCl salt) (Et_2O/MeOH) 214-216°C	(2·HCl salt) 3405, 2940, 2554, 1625, 1463, 1402, 1250, 1145, 1092, 752, 702	1.41 (6H, s), 1.67-2.30 (4H, m), 2.07 & 2.08 & 2.11 & 2.13 (12H, each s), 2.19 (2H, m), 2.58 (2H, m), 2.80 (2H, m), 2.90 & 3.35 (3H, each s), 3.09 (2H, m), 3.46 (2H, brs), 4.54 & 4.86 (1H, each m), 7.17-7.31 (5H, m),
29		white powder (2·HCl salt) (Et_2O/MeOH) 245-247°C	(2·HCl salt) 3410, 2928, 2634 1638, 1603, 1496 1462, 1415, 1323 1250, 1102, 703	(2·HCl salt: CD_3OD) 1.89-2.27 (4H, m), 2.23&2.25&2.31&2.34 (12H, each s), 2.87&2.92 (3H, each s), 3.06-3.40 (6H, m), 3.69-3.79 (2H, m), 3.85&4.66 (1H, m), 4.88&5.00 (2H, each s), 7.31 (5H, m)

Table 6:

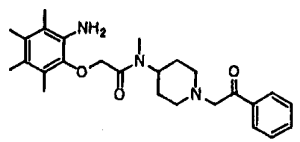
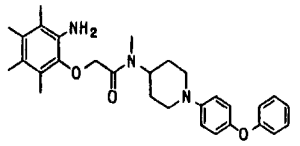
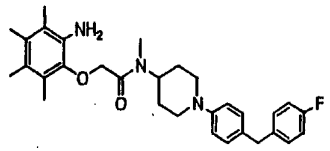
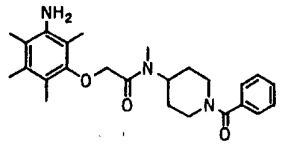
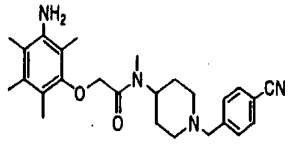
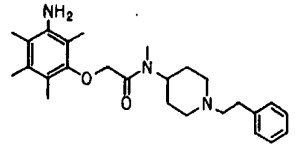
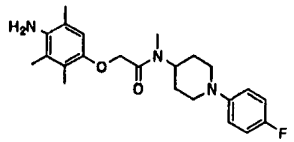
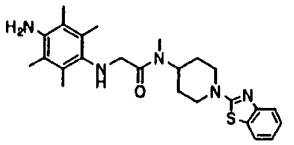
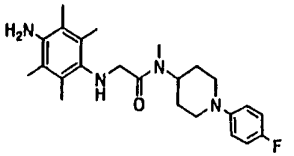
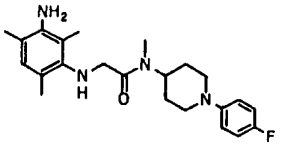
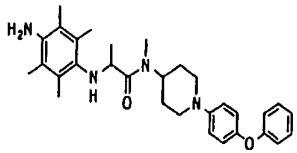
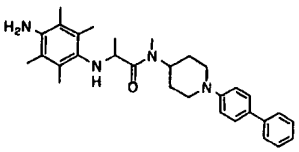
No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
30		pale yellow powder (2·HCl salt) (Et_2O/MeOH) 169-171°C	(2·HCl salt) 3435, 2934, 2618 1694, 1639, 1598 1451, 1232, 1102 757	1.44-1.70 (2H, m), 1.81-2.34 (4H, m), 2.10 (3H, s), 2.13 (3H, s), 2.17(3H, s), 2.22&2.23 (3H, each s), 2.77&2.92 (3H, each s), 3.10 (2H, m), 3.37&4.58 (1H, m), 3.82&3.85 (2H, each s), 4.16 (2H, brs), 4.47&4.51 (2H, each s), 7.46 (2H, t), 7.58 (1H, t), 7.98 (2H, d)
31		white powder (2·HCl salt) (Et_2O/MeOH) 164-166°C	(2·HCl salt) 3396, 2888, 2614 1641, 1588, 1508 1490, 1247, 1173 1098	1.72-2.09 (4H, m), 2.11 (3H, s), 2.14 (3H, s), 2.18 (3H, s), 2.23 (3H, s), 2.70&2.85 (2H, m), 2.79&2.95 (3H, each s), 3.49&4.69 (1H, m), 3.66 (2H, m), 4.19 (2H, brs), 4.50&4.54 (2H, each s), 6.88-7.08 (6H, m), 7.24-7.33 (3H, m)
32		pale yellow powder (2·HCl salt) (Et_2O/MeOH) 165-167°C	(2·HCl salt) 3410, 2916, 2614 1639, 1508, 1414 1323, 1221, 1158 820	1.69-2.07 (4H, m), 2.10 (3H, s), 2.14 (3H, s), 2.17 (3H, s), 2.23 (3H, s), 2.68&2.83 (2H, m), 2.77&2.92 (3H, each s), 3.49&4.68 (1H, m), 3.70 (2H, m), 3.87 (2H, s), 4.20 (2H, brs), 4.49&4.53 (2H, each s), 6.82-6.92 (2H, m), 6.95 (2H, t), 7.05 (2H, d), 7.08-7.16 (2H, m)
33		white powder (HCl salt) (Et_2O/MeOH) 171-174°C	(HCl salt) 3423, 2934, 2577, 1626, 1518, 1447, 1318, 1279, 1250, 1107, 1025, 711	(2·HCl salt) : CD_3OD 1.81 (4H, m), 2.26 & 2.29 & 2.32 (12H, each s), 2.90 & 2.92 (3H, each s), 2.91 & 3.25 & 3.82 (4H, each m), 4.50 & 4.59 (2H, each s), 4.75 (1H, m), 7.46(5H, m),
34		white powder (2·HCl salt) (Et_2O/MeOH) 203-205°C	(2·HCl salt) 3406, 2936, 1637, 1460, 1418, 1322, 1305, 1249, 1096, 1031, 944, 827	1.59-2.22 (6H, m), 2.09 & 2.13 & 2.18 (12H, each s), 2.90 (2H, s), 2.88 & 2.92 (3H, each m), 3.54 (4H, brs), 3.67 & 4.55 (1H, each m), 4.34 & 4.37 (2H, each s), 7.43 (2H, m), 7.60 (2H, m),
35		white powder (2·HCl salt) (Et_2O/MeOH) 157-158°C	(2·HCl salt) 3421, 2940, 1638, 1492, 1457, 1420, 1312, 1248, 1099, 1032, 703	1.69-2.23 (4H, m), 2.09 & 2.14 & 2.18 (12H, each s), 2.60 (2H, m), 2.79 (2H, m), 2.87 & 2.92 (3H, each s), 3.08 (2H, m), 3.49 (2H, brs), 3.66 & 4.58 (1H, each m), 4.35 & 4.38 (2H, each s), 7.18-7.31 (5H, m)

Table 7:

No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
36		white powder (2·HCl salt) (Et_2O/MeOH) 198-200°C	(2·HCl salt) 3454, 2950, 2359 1655, 1514, 1492 1414, 1291, 1238 1134, 1101	1.70-2.09 (4H, m), 2.11 (3H, s), 2.16 (3H, s), 2.17&2.21 (3H, each s), 2.68-2.87 (2H, m), 2.89&2.96 (3H, each s), 3.37 (2H, brs), 3.60 (2H, m), 3.98&4.54-4.68 (1H, m), 4.59&4.64 (2H, each s), 6.56&6.61 (1H, each s), 6.83-7.00 (4H, m)
37		white powder (2·HCl salt) (Et_2O/MeOH) 190-194°C	(2·HCl salt) 3424, 2929, 1624, 1540, 1468, 1412, 1262, 1126, 1095, 1018, 762	(2·HCl salt) ; DMSO 1.65-1.87 (4H, m), 2.17 (6H, s), 2.22 (3H, s), 2.24 (3H, s), 2.77 & 2.80 (3H, each s), 3.30 (2H, m), 3.96 (2H, s), 4.13 (2H, m), 4.59 (1H, m), 7.10 (1H, dd), 7.30 (1H, dd), 7.47 (1H, d), 7.78 (1H, d)
38		pale yellow foam (2·HCl salt) (Et_2O/MeOH) 231-235°C	(2·HCl salt) 3420, 1651, 1511, 1451, 1407, 1237, 1166, 1101, 1012, 844	1.67-2.04 (4H, m), 2.13 (6H, s), 2.29 (6H, s), 2.65 & 2.82 (2H, each m), 2.77 & 2.92 (3H, each s), 3.46 (2H, m), 3.61 & 3.66 (2H, each s), 4.70 (1H, m), 6.88-6.98 (4H, m)
39		white powder (2·HCl salt) (Et_2O/MeOH) 193-195°C	(2·HCl salt) 3418, 2846, 2590 1638, 1575, 1513 1488, 1409, 1358 1238, 1104	1.63-2.07 (4H, m), 2.10&2.12&2.19&2.25&2.26 (9H, each s), 2.58-2.86 (2H, m), 2.78&2.92 (3H, each s), 3.38-3.55&4.65 (1H, m), 3.48 (2H, brs), 3.60 (2H, m), 3.72&3.76 (2H, each s), 4.53 (1H, brs), 6.68&6.75 (1H, each s), 6.84-7.00 (4H, m)
40		white powder (2·HCl salt) (Et_2O/MeOH) 197-200°C	(2·HCl salt) 3365, 2928, 2470 1638, 1588, 1507 1488, 1248, 1200 1112, 1074	1.23&1.32 (3H, each d), 1.41-1.98 (4H, m), 2.10 (3H, s), 2.11 (3H, s), 2.24 (3H, s), 2.27 (3H, s), 2.55-2.88 (2H, m), 2.71&2.79 (3H, each s), 3.29-3.68 (4H, m), 3.45&4.62 (1H, m), 3.97 (1H, m), 6.84-7.33 (9H, m)
41		white powder (2·HCl salt) (Et_2O/MeOH) 175-177°C	(2·HCl salt) 3384, 2922, 2478, 1638, 1573, 1486, 1452, 1393, 1364, 1335, 1075	(2·HCl salt) : CD_3OD 1.23&1.33 (3H, each d), 1.45-1.99 (4H, m), 2.10 (3H, s), 2.11 (3H, s) 2.24 (3H, s), 2.27 (3H, s), 2.33-2.95 (2H, m), 2.70& 2.79 (3H, each s), 3.30-3.85 (4H, m), 3.47&4.66 (1H, m), 3.97 (1H, m), 6.92-7.03 (2H, m), 7.24-7.34 (3H, m), 7.40 (1H, m), 7.47-7.59 (3H, m)

The effect of aminophenoxyacetamide derivatives of the present invention represented by the formula (I) was evaluated by the following biological testing methods.

Test 1: Evaluation for neuroprotective effect against glutamate induced neurodegeneration, by comparing the administration of the test compound prior to the glutamate addition with the simultaneous administration of the test compound along with the glutamate.

Test 2: Evaluation for antagonism against cell death by treatment of various kinds of receptor inhibitor and MTA [5-deoxy-5-methyl-thioadenosine].

Test 3: Evaluation for CalbindinD-28k production increasing effect.

Test 4: Evaluation for neuroprotective inhibiting effect by antisense oligonucleotide.

Test 5: Evaluation for cerebral edema suppressing effect.

By using of the above-mentioned biological tests, the selection of the compounds having neuroprotective effect by activating the receptor of FGF, due to the introduction of the CalbindinD-28k, one of Ca^{2+}-binding proteins, was performed by combining all the Test 1 to 4, by combining Test 1 and 2, by combining Test 1, 2 and 3, or by combining Test 1, 3,and 4, respectively.

The following are the detailed description of the test methods.

Biological test 1: Evaluation for neuroprotective effect against glutamate induced neuronal cell death

Primary cultures were prepared from cerebral cortices of fetal Wistar rats (E18) according to the modified method of

Mattson and Kater [M. P. Mattson, *Brain Res. Rev.*, 13, 179 (1988)]. After papain-dissociation, neurons were seeded on poly-L-lysine coated 96 wells plates (Sumitomo Bakelite Co., Ltd.) at density of 5 x 10^4 cells/well and cultivated in 100 µl of DMEM medium (Dulbecco's modified Eagle medium (Gibco) supplemented with 10 mM $NaHCO_3$, 15 mM KCl, 1 mM sodium pyruvate, and 10% (vol/vol) horse serum). Cultures were maintained at 37 C in a 90% air/10% CO_2 humidified incubator. Glutamate was added to the culture at day 4 to the final concentration of 1 mM. Cell survival was then determined 1 day later by using 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT). MTT was dissolved in phosphate buffered saline (PBS, pH 7.4) at 5 mg/ml and filtered to sterilize and remove a small amount of insoluble residue present in some batches of MTT, and added to the cultures at a final concentration of 0.5 mg/ml. Six hours after incubation, culture medium was discarded to stop the reaction. Dimethyl sulfoxide was added to all wells and mixed thoroughly to dissolve the dark blue crystals. After a few minutes at room temperature, the plates were read by using Micro ELISA Reader at a test wavelength of 570 nm and a reference wavelength of 650 nm.

The test compounds (1 µM) was added 24 hrs prior to glutamate treatment and simultaneously with glutamate.

The effect of the test compounds was determined as the survival rate of living cells (%) according to the following equation:

Survival rate of living cells (%) =
[(test compound group - glutamic acid treated group) ÷
(control group - glutamic acid treated group)] x 100

That is, the survival rate of living cells after

incubation of the control group was converted to 100 %, and the survival rate of living cells of the tested compounds was calculated.

Biological test 2: Evaluation for antagonism against neuronal cell death by treatment of various kinds of receptor inhibitor of physiological active substances and MTA

This biological test is performed to determine whether the neuroprotective effect of the test compounds is due to the activation of receptors of physiological active substances or not, by using antagonistic test for neutralizing antibody and inhibitor for FGF, NT-3, NT-4/5, BDNF, IGF-I/II, NGF, PDGF and estrogen, respectively.

MTA (5-deoxy-5-methylthioadenosine) specifically inhibits the autophosphorylation of FGF receptor in the living cells [P.A. Mather, *J. Bio. Chem.*, 268, 4244 (1993)]. Therefore, the neuroprotective effect of the test compounds is inhibited by treatment of MTA, this effect is depended by the signal transfer effect through the phosphorylation of FGF receptor.

The inhibitors of the various kinds of receptor were dissolved in the optimum concentration, and MTA was dissolved in the concentration of 7.5 mM, just before the using. 30 minutes before the treatment of the test compounds, the optimum concentration of each inhibitors or 0.75 mM of MTA was added, and the neuroprotective effect of the test compounds was determined by mean of MTT method.

The results of each Biological Test 1 and 2 were shown in the following Table 8.

Table 8

Compound No.	Survival Rate (%) (Compound: 1 μl)	Survival Rate (%) (Compound: 1 μl & MTA treatment)
6	54	25
7	76	32
8	78	24
9	104	5
10	86	31
11	74	56
12	54	33
13	65	13
16	101	33
17	85	55
18	91	57
19	96	28
22	79	32
24	61	22
25	87	16
28	103	46
32	73	34
33	120	46
34	74	21
36	97	25
37	95	20
38	124	19
39	94	28

Biological test 3: Evaluation for CalbindinD-28k inducing effect

Primary cultures were prepared from cerebral cortices of fetal Wistar rats (E18) according to the modified method of Mattson and Kater[M. P. Mattson, *Brain Res. Rev.*, 13, 179 (1988)]. After papain-dissociation, neurons were seeded on poly-L-lysine coated 6 wells plates (Falcon) at density of 5500 cells/mm^2 and cultivated in 2 ml of DMEM medium.

Test compounds were added 5 days after initiation of the incubation, and after 7 days of incubation, the protein was extracted with homogenized buffer solution [containing 20 mM of Tris-HCl (pH=7.4), 1 mM of EDTA, and 0.1 mM of phenylmethyl-sulfonyl fluoride].

The effect of the test compounds was determined by the western blot technique using polyclonal anti CalbindinD-28k Swant (Swant Co., Ltd.) as antibody.

Table 9 shows the test results. In the table, the amount of induced CalbindinD-28k of the control group (none-treated group) was indicated as 100 percents.

Table 9:

Compound No.	Amount of induced CalbindineD-28k (% vs. control) (Compound: 1 μM)
6	163
Control	100

Biological test 4: Evaluation for neuroprotective inhibiting effect by antisense oligonucleotide

It is necessary to produce the protective protein for the signal transfer action of cells through the phosphorylation of FGF receptor for the neuroprotective effect of the test compounds, and the CalbindinD-28k is one of that protective proteins having Ca^{2+} buffering function. Therefore, the following test determined whether CalbindinD-28k is concerned in the neuroprotective effect of the test compounds by using an antisense oligonucleotide.

Primary cultures were prepared from cerebral cortices of fetal Wistar rats (E18). After papain-dissociation, neurons were seeded on poly-L-lysine coated 96 wells plates (Sumitomo Bakelite Co., Ltd.) at density of $4x10^4$ cells/well and cultivated in 100 μl of DMEM medium.

From 2 days after the incubation to 8 days, 100 μl of Neurobasal medium/2% B-27 Supplement and 5 μM of three kinds of antisense oligonucleotides were added respectively, on every 24 hours. 7 days after incubation, 1 μM and 10 μM of the test compounds were added, and 8 days after incubation, 300 μM of

glutamic acid was added. Cell survival was then determined 1 day later by using MTT. Six hours after incubation, culture medium was discarded to stop the reaction. Dimethyl sulfoxide was added to all wells and mixed thoroughly to dissolve the dark blue crystals. After a few minutes at room temperature, the plates were read by using Micro ELISA Reader at a test wavelength of 570 nm and a reference wavelength of 650 nm.

The effect of the test compounds was determined as the survival rate of living cells (%) according to the equation as indicated in the Biological Test 1: That is, the survival rate of living cells after incubation of the control group was converted to 100 %, and the survival rate of living cells of the tested compounds was calculated.

The sequences of the antisense oligonucleotides to be used in this test are following.

calbindin antisense 1: 5-TGA CTG CAG GTG GGA TTC TGC-3

calbindin antisense 2: 5-ACC GTC GAA ATG AAG CCA GA-3

calbindin antisense 3: 5-CGT ATC ATC CAC GGT CTT GTT-3

Table 10 shows the test results.

Table 10:

Test Compound	Survival Rate (%) [antisense (-)]	Survival Rate (%) [antisense (+): 5 μM]
BFGF (1 ng)	71	8
BFGF (10 ng)	101	35
No. 6 (0.1 μM)	103	30
No. 6 (1 μM)	108	34
No. 38 (0.1 μM)	100	28
No. 38 (1 μM)	106	33

Biological test 5: Evaluation for cerebral edema suppressing effect

Adult male Wistar rats weighing 210-230 g were used in the present study and housed in an artificially controlled environment with 12-hour light/dark cycle. Animals were anesthetized with pentobarbital sodium (50 mg/kg of body weight, i.p., Nembutal, Dinabbott, Japan) and placed in a stereotaxic apparatus. The skull was exposed and a hole was made on the parietal bone; 1.5 mm posterior and 0.8 mm lateral to the bregma. All procedures were performed under a surgery microscope to avoid excess irritation to the meninges and the underlying brain. A brass screw with a blunt tip (1.0 mm in diameter and 3.0 mm in length, Biomedica, Japan) was inset in the hole. The screw tip protruding intracranially was approximately 2.5 mm, which stuck into the parietal part of the right cerebrum through the meninges. In sham-operated rats, scalp was closed without attaching a screw to the hole. After surgery, all rats were kept in their original dens until sacrifice. Rats were allowed to feed chow and water *ad libitum*.

Under anesthesia the rat cerebral hemispheres of the target were processed for water content on post-TBI day 6 (n=6). The cerebral hemispheres dissected out were weighed, dried for 24 hours at 110 degree (Celsius) and then weighed again. The subtracted amount of the wet and dry weights was regarded as tissue water of the target, and utilized for the analysis of the cerebral edema.

The water content was calculated by using the following formula:

Water content (%) = [(wet weight of hemisphere - dry weight of hemisphere) / wet weight of hemisphere] x 100

The test compounds were intravenously administered just

after the operation via tail vein of the rats.

Table 11 shows the test results.

Table 11:

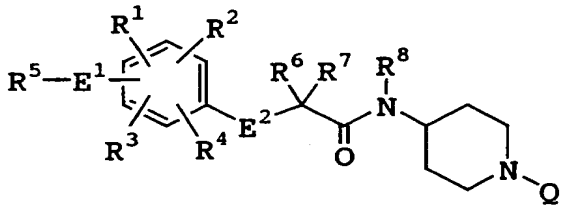
Compound No. (administration amount)	Cerebral edema suppressing rate (%)
6 (3 mg/kg)	24.9
8 (1 mg/kg)	14.0
12 (3 mg/kg)	14.7
13 (3 mg/kg)	13.1
14 (1 mg/kg)	18.7
15 (1 mg/kg)	14.7
18 (1 mg/kg)	22.1
24 (1 mg/kg)	10.6
25 (1 mg/kg)	19.1
26 (3 mg/kg)	11.9
27 (3 mg/kg)	11.8
29 (1 mg/kg)	13.8

INDUSTRIAL APPLICABILITY

As described above, the present invention provides lower molecular compounds, especially aminophenoxyacetamide derivatives of the formula (I), which induce the CalbindinD-28k, one of Ca^{2+}-binding proteins, and can be easily administrated. Since the induction of CalbindinD-28k caused by the administration of the compound provided by the present invention cause neuroprotective effect and cerebral functional and organic disorder improving and treating effect, it can be understood that the agent of the present invention is highly applicable in pharmaceutical field.

CLAIMS

1. An aminophenoxyacetamide derivative represented by the following formula (I):



(I)

wherein:

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom or lower alkyl group;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom or lower alkyl group;

E^1 is group $-NR^9-$ (in which, R^9 is hydrogen atom or lower alkyl group);

E^2 is oxygen atom or group $-NR^{10}-$ (in which, R^{10} is hydrogen atom or lower alkyl group which may be substituted);

Q is a group of -X-Y-Q', wherein X is a connecting bond, lower alkyl group, lower alkenyl group, or lower alkynyl group; Y is a connecting bond, or a group selected from the groups consisting of C=O, C(=O)NH, NHC(=O), -O-, -S-, CH(OH), -O-CH(OH)- and $-O-CH_2-CH(OH)-$, in which hydrogen atom of amido group may be substituted with lower alkyl group; and Q' is hydrogen atom or a cyclic group selected from the groups consisting of aryl group, heteroaryl group, saturated or unsaturated cyclic hydrocarbon group, and saturated or unsaturated heterocyclic group, wherein one or more of the hydrogen atoms in the cyclic group of Q' may be substituted;

either in the case that X and Y are both connecting bond then Q' is not hydrogen atom; or in the case that one of X and Y is other than connecting bond then E^2 is the group -O- and all of

the groups of R^1, R^2, R^3 and R^4 are not hydrogen atom;
or a pharmaceutically acceptable salt thereof.

2. The aminophenoxyacetamide derivative of formula (I) claimed in claim 1, wherein X and Y are both connecting bond;
or pharmaceutically acceptable salts thereof.

3. The aminophenoxyacetamide derivative of formula (I) claimed in claim 1, wherein, one of X and Y is other than connecting bond and E^2 is the group -O- and all of the groups of R^1, R^2, R^3 and R^4 are other than hydrogen atom, wherein X, Y, R^1, R^2, R^3 and R^4 are the same as defined above in claim 1;
or pharmaceutically acceptable salts thereof.

4. Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

5. Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 2, as an active ingredient.

6. Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3, as an active ingredient.

7. Induction agent of the production of CalbindinD-28K, which is Ca^{2+}-binding proteins, containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

8. Induction agent of the production of CalbindinD-28K, which is Ca^{2+}-binding proteins, containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

9. Induction agent of the production of CalbindinD-28K, which is Ca^{2+}-binding proteins, containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3, as an active ingredient.

10. A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

11. A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

12. A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3, as an active ingredient.

13. Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis,

which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

14. Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

15. Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3, as an active ingredient.

16. A method for selecting neuroprotective compound, in which said method is evaluating the activation of receptor of various kinds of physiological active substances and the phosphorylation of FGF receptor, due to the induction of the CalbindinD-28k production.

17. The method for selecting neuroprotective compound according to claim 16, in which said method is evaluating the

autophosphorylation of FGF receptor.

18. The method for selecting neuroprotective compound according to claim 16, wherein said method is performed by combining all the Test 1 to 4, by combining Test 1 and 2, by combining Test 1, 2 and 3, by combining Test 1 and 3, or by combining Test 1, 3,and 4, respectively, wherein each of the Test 1 to 4 is consisting of the following method respectively;

Test 1: Evaluation for neuroprotective effect of the compound against glutamate-induced neurodegeneration,

Test 2: Evaluation for antagonism against neuroprotective effect of compounds by treatment of MTA [5-deoxy-5-methyl-thioadenosine], which inhibit autophosphorylation of FGF receptor, and for antagonism by treatment of inhibitor of various physiological active substance receptors such as neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I/II (IGF-I/II), platelet-derived growth factor (PDGF), estrogen, to determine the neuroprotective effect is due to autophosphorylation of receptors of FGF receptor,

Test 3: Evaluation for CalbindinD-28k inducing effect on the compound, and

Test 4: Confirmation for the neuroprotective effect of the compound is due to inducing capability of the CalbindinD-28k production, by the treatment of antisense oligonucleotide of CalbindinD-28k.

19. Neuroprotective compounds selected by the method according to any one of claims 16 to 18.

20. Medicament containing neuroprotective compounds according

to claim 19.

21. The medicament according to claim 20 for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

10/009566

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SN-48		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 01/ 03198	13/04/2001	13/04/2000
Applicant		
SUNTORY LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 01/03198

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 19-21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19-21

Claims 19-21 relate to neuroprotective compounds defined by reference to a desirable characteristic or property, namely being selected by the method according ro any one of claims 16 to 18.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for the compounds claimed in claims 1-3, on which a search has already been performed.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the subject-matter of claims 19-21 going beyond the above-mentioned compounds is impossible. Consequently, no search has been performed on these claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 01/03198

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/15 C07D211/58 C07D417/04 A61K31/4468 A61P25/00
G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 23076 A (SUNTORY LTD ;URAMOTO HIROSHI (JP); ANNOURA HIROKAZU (JP); TAKEMOTO) 27 April 2000 (2000-04-27) the whole document	1-18
A	EP 0 982 026 A (HOFFMANN LA ROCHE) 1 March 2000 (2000-03-01) example 79	1,4-16, 19,20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2002	22.03.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pellegrini, P

3

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/JP 01/03198

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BOUILLON R ET AL: "Antagonistic activity of 24-oxa-analogs of vitamin D" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 60, no. 6, 1 June 1995 (1995-06-01), pages 484-490, XP004026517 ISSN: 0039-128X paragraph "intrinsic activity" page 487, right-hand column	1,4-16, 19,20
A	MCMAHON ANNE ET AL: "Calbindin-D28k buffers intracellular calcium and promotes resistance to degeneration in PC12 cells." MOLECULAR BRAIN RESEARCH, vol. 54, no. 1, February 1998 (1998-02), pages 56-63, XP001064171 ISSN: 0169-328X abstract page 59, column 2, paragraph 3 page 63, column 1, paragraph 2	16-18
A	NG MAY C ET AL: "The neurotoxin MPTP increases calbindin-D-28k levels in mouse midbrain dopaminergic neurons." MOLECULAR BRAIN RESEARCH, vol. 36, no. 2, 1996, pages 329-336, XP001064172 ISSN: 0169-328X abstract	16-18
A	MASUMURA MAKOTO ET AL: "Selective induction of fibroblast growth factor receptor-1 mRNA after transient focal ischemia in the cerebral cortex of rats." NEUROSCIENCE LETTERS, vol. 213, no. 2, 1996, pages 119-122, XP001064173 ISSN: 0304-3940 abstract	16-18

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 01/03198

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0023076 A	27-04-2000	AU 6122699 A	08-05-2000
		CN 1287487 T	14-03-2001
		EP 1045693 A1	25-10-2000
		HU 0100819 A2	28-08-2001
		WO 0023076 A1	27-04-2000
EP 0982026 A	01-03-2000	EP 0982026 A2	01-03-2000
		AU 4453799 A	04-05-2000
		BR 9903779 A	19-09-2000
		CN 1248439 A	29-03-2000
		HR 990256 A1	30-04-2000
		HU 9902737 A2	28-06-2000
		JP 2000109429 A	18-04-2000
		NO 993948 A	21-02-2000
		PL 334949 A1	28-02-2000
		TR 9902015 A2	21-03-2000
		US 6184236 B1	06-02-2001
		ZA 9905212 A	18-02-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

KUSAMA, Osamu
KUSAMA PATENT OFFICE
7F Iwata Bldg., 5-12, Iidabashi 4-chome
Chiyoda-ku, Tokyo 102-0072
JAPON

Date of mailing (day/month/year)	**IMPORTANT NOTIFICATION**
18 May 2001 (18.05.01)	
Applicant's or agent's file reference	**International application No.**
SN-48	PCT/JP01/03198

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SUNTORY LIMITED (for all designated States except US)
TAKEMOTO, Naohiro et al (for US)

International filing date	:	13 April 2001 (13.04.01)
Priority date(s) claimed	:	13 April 2000 (13.04.00)
Date of receipt of the record copy by the International Bureau	:	27 April 2001 (27.04.01)
List of designated Offices	:	

EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
National :AU,CA,CN,HU,JP,KR,US

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [X] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Masashi HONDA

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

KUSAMA, Osamu
KUSAMA PATENT OFFICE
7F, Iwata Bldg., 5-12, Iidabashi 4-chome
Chiyoda-ku, Tokyo 102-0072
JAPON

Date of mailing (day/month/year) 18 May 2001 (18.05.01)	
Applicant's or agent's file reference SN-48	**IMPORTANT NOTIFICATION**
International application No. PCT/JP01/03198	International filing date (day/month/year) 13 April 2001 (13.04.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 13 April 2000 (13.04.00)
Applicant SUNTORY LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
13 Apri 2000 (13.04.00)	2000-112100	JP	27 Apri 2001 (27.04.01)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Masashi HONDA

Telephone No. (41-22) 338.83.38

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PCT REQUEST

SN-48

Original (for **SUBMISSION**) - printed on 13.04.2001 02:38:41 PM

0	**For receiving Office use only**	
0-1	International Application No.	PCT 13.4.01 受領印
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form - PCT/RO/101 PCT Request**	
0-4-1	Prepared using	**PCT-EASY Version 2.91 (updated 01.01.2001)**
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	**Japanese Patent Office (RO/JP)**
0-7	**Applicant's or agent's file reference**	**SN-48**
I	**Title of invention**	**AMINOPHENOXYACETAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITION CONTAINING THEREOF**
II	**Applicant**	
II-1	This person is:	**applicant only**
II-2	Applicant for	**all designated States except US**
II-4	Name	**SUNTORY LIMITED**
II-5	Address:	**1-40, Dojimahama 2-chome, Kita-ku, Osaka-shi, Osaka 530-8203 Japan**
II-6	State of nationality	**JP**
II-7	State of residence	**JP**
II-8	Telephone No.	**03-5210-5002**
II-9	Facsimile No.	**03-5210-5067**
III-1	**Applicant and/or inventor**	
III-1-1	This person is:	**applicant and inventor**
III-1-2	Applicant for	**US only**
III-1-4	Name (LAST, First)	**TAKEMOTO, Naohiro**
III-1-5	Address:	**4-5-305, Nishichujo-cho, Ibaraki-shi, Osaka 567-0887 Japan**
III-1-6	State of nationality	**JP**
III-1-7	State of residence	**JP**

PCT REQUEST SN-48

Original (for **SUBMISSION**) - printed on 13.04.2001 02:38:41 PM

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ANNOURA, Hirokazu
III-2-5	Address:	16-8, Kitashinotani, Chohoji, Nagaokakyo-shi, Kyoto 617-0812 Japan
III-2-6	State of nationality	JP
III-2-7	State of residence	JP
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	MURAYAMA, Norihito
III-3-5	Address:	9-5-507, Yamazaki 1-chome, Shimamoto-cho, Mishima-gun, Osaka 618-0001 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	KUSAMA, Osamu
IV-1-2	Address:	KUSAMA PATENT OFFICE 7F Iwata Bldg., 5-12, Iidabashi 4-chome, Chiyoda-ku, Tokyo 102-0072 Japan
IV-1-3	Telephone No.	03-3263-1281
IV-1-4	Facsimile No.	03-3263-1280
IV-1-5	e-mail	IZK00360@nifty.ne.jp
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AU CA CN HU JP KR US

PCT REQUEST SN-48

Original (for **SUBMISSION**) - printed on 13.04.2001 02:38:41 PM

V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	13 April 2000 (13.04.2000)	
VI-1-2	Number	Patent application 2000-112100	
VI-1-3	Country	JP	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	52	-
VIII-3	Claims	6	-
VIII-4	Abstract	1	EZABST00.TXT
VIII-5	Drawings	1	-
VIII-7	TOTAL	64	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-12	Priority document(s)	Item(s) VI-1	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-17	Other (specified):	Revenue stamps of transmittal fee for receiving office	-
VIII-17	Other (specified):	Submission of certificate of payment for search fee	-
VIII-17	Other (specified):	Submission of certificate of payment for international fee	-
VIII-18	**Figure of the drawings which should accompany the abstract**	1	
VIII-19	**Language of filing of the international application**	English	

PCT REQUEST SN-48

Original (for **SUBMISSION**) - printed on 13.04.2001 02:38:41 PM

IX-1	**Signature of applicant or agent**	
IX-1-1	Name (LAST, First)	KUSAMA, Osamu

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PCT (ANNEX - FEE CALCULATION SHEET)

SN-48

Original (for **SUBMISSION**) - printed on 13.04.2001 02:38:41 PM

(This sheet is not part of and does not count as a sheet of the international application)

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	**Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet**				
0-4-1	Prepared using		PCT-EASY Version 2.91 (updated 01.01.2001)		
0-9	**Applicant's or agent's file reference**		SN-48		
2	**Applicant**		SUNTORY LIMITED, et al.		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (JPY)	
12-1	Transmittal fee	T	⇨	18,000	
12-2	Search fee	S	⇨	103,000	
12-3	International fee Basic fee (first 30 sheets)	b1	46,200		
12-4	Remaining sheets		34		
12-5	Additional amount	(X)	1,100		
12-6	Total additional amount	b2	37,400		
12-7	b1 + b2 =	B	83,600		
12-8	Designation fees Number of designations contained in international application		8		
12-9	Number of designation fees payable (maximum 6)		6		
12-10	Amount of designation fee	(X)	10,000		
12-11	Total designation fees	D	60,000		
12-12	PCT-EASY fee reduction	R	-14,000		
12-13	Total International fee (B+D-R)	I	⇨	129,600	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	250,600	
12-19	**Mode of payment**		Transmittal fee: revenue stamps Search fee: bank draft International fee: bank draft Priority document fee:		

VALIDATION LOG AND REMARKS

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
KUSAMA, Osamu
KUSAMA PATENT OFFICE
7F, Iwata Bldg., 5-12, Iidabashi 4-chome
Chiyoda-ku, Tokyo 102-0072
JAPON

Date of mailing (day/month/year)	
25 October 2001 (25.10.01)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
SN-48	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/JP01/03198	13 April 2001 (13.04.01)	13 April 2000 (13.04.00)

Applicant
SUNTORY LIMITED et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
   KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AU,CA,CN,EP,HU,JP

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on
   25 October 2001 (25.10.01) under No. WO 01/79170

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

13.12.30

To:
KUSAMA PATENT OFFICE
Attn. Kusama, Osamu
7F Iwata Bldg., 5-12, Iidabashi
4-chome, Chiyoda-ku
Tokyo 102-0072
JAPAN

Date of mailing *(day/month/year)* 15/11/2001	
Applicant's or agent's file reference SN-48	**PAYMENT DUE** within 45 ~~months~~/days from the above date of mailing
International application No. PCT/JP 01/03198	International filing date *(day/month/year)* 13/04/2001
Applicant SUNTORY LIMITED	

1. This International Searching Authority

(i) considers that there are 2 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
1-15

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

EUR 945,00	x	1	=	EUR 945,00
Fee per additional invention		number of additional inventions		total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [ ] Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ralf Ockers

Form PCT/ISA/206 (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/JP 01/03198

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15

   4-aminopiperidines of Formula I and their use as CalbindinD-28k inducers

2. Claims: 16-21

   A method to screen compounds which stimulate the production of calbindinD-28k

(D1) (Steroids (1995) 60, page 484-90) shows that anologs of Vitamin D, which are low molecular-weight compounds, induce CalbindinD-28k production.

It is furthermore generally known that calbindinD-28k inducive compounds are neuroprotective (see page 2, lines 13-29).

The single general inventive concept, as stated in Rule 13.1 PCT, is the notion that lower molecular-weight compounds which stimulate the production of CalbindinD-28k are neuroprotective compounds.

The problem to be solved over (D1) is to provide further low molecular weight neuroprotective compounds capable of inducing the production of CalbindinD-28k (see e.g. description page 3 lines 25-28).

This problem is solved in two ways in the present application:

1. by providing the compounds of claim 1
2. by providing the screening method described in claims 16-21.

As (D1) already provides low molecular weight compounds which induce CalbindinD-28k and as the technical link between CalbindinD-28k and neuroprotective activity is part of the common knowledge of the person skilled in the art, the above single general concept cannot be considered to be the single general inventive concept of Rule 13.1 PCT.

Moreover: the special technical features of subject 1 (the compounds of claim 1) do not appear as the same or corresponding features of claim 2 (the screening method of claims 16-21).

Consequently, the application lacks unity of invention within the meaning of Rule 13.1 PCT. The application therefore splits into two inventions.

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/JP 01/03198

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
1-15
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 23076 A (SUNTORY LTD ;URAMOTO HIROSHI (JP); ANNOURA HIROKAZU (JP); TAKEMOTO) 27 April 2000 (2000-04-27) the whole document	1-16
A	EP 0 982 026 A (HOFFMANN LA ROCHE) 1 March 2000 (2000-03-01) example 79	1,4-16, 19,20
A	BOUILLON R ET AL: "Antagonistic activity of 24-oxa-analogs of vitamin D" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 60, no. 6, 1 June 1995 (1995-06-01), pages 484-490, XP004026517 ISSN: 0039-128X paragraph "intrinsic activity" page 487, right-hand column	1,4-16, 19,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Form PCT/ISA/206 (Annex, first sheet) (July 1992)

Patent Family Annex

[redacted]ation on patent family members

[redacted]rnational Application No
PCT/JP 01/03198

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0023076 A	27-04-2000	AU 6122699 A	08-05-2000
		CN 1287487 T	14-03-2001
		EP 1045693 A1	25-10-2000
		HU 0100819 A2	28-08-2001
		WO 0023076 A1	27-04-2000
EP 0982026 A	01-03-2000	EP 0982026 A2	01-03-2000
		AU 4453799 A	04-05-2000
		BR 9903779 A	19-09-2000
		CN 1248439 A	29-03-2000
		HR 990256 A1	30-04-2000
		HU 9902737 A2	28-06-2000
		JP 2000109429 A	18-04-2000
		NO 993948 A	21-02-2000
		PL 334949 A1	28-02-2000
		TR 9902015 A2	21-03-2000
		US 6184236 B1	06-02-2001

The PTO did not receive the following listed item(s) No Postcard

(Translation)

PATENT OFFICE

JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this office.

Date of Application: April 13, 2000

Application Number: Patent Application No. 2000-112100

Applicant(s): SUNTORY LIMITED

March 23, 2001

Kozo OIKAWA
Commissioner, Patent Office

Application Certified No.: Appln. Cert. Pat. 2001-3023042

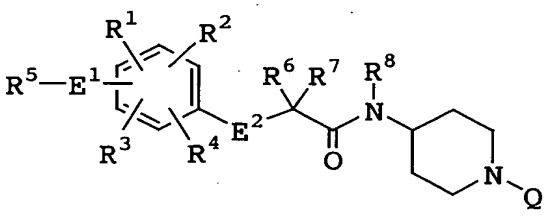
【Name of the Document】 DESCRIPTION

【Name of the Invention】 MINOPHENOXYACETAMIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITION CONTAINING THEREOF

【Claims】

【Claim 1】 An aminophenoxyacetamide derivative represented by the following formula (I):

【Formula 1】



(I)

wherein:

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; hydroxy group; alkoxy group; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substi-tuted; or aralkyl group which may be substituted;

E^1 is oxygen atom; sulfur atom; or group $-NR^9-$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

E^2 is oxygen atom; sulfur atom; or group $-NR^{10}-$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

Q is aryl group which may be substituted;

(provided that both E^1 and E^2 do not represent oxygen atom or sulfur atom at the same time);

or a pharmaceutically acceptable salt thereof.

[Claim 2] The aminophenoxyacetamide derivative of formula (I) claimed in claim 1, wherein,

R^1, R^2, R^3 and R^4 all are methyl group;

when E^1 is oxygen atom; E^2 is the group $-NR^9-$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted); or when E^1 is group $-NR^{10}-$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted); E^2 is oxygen atom;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

Q is group $-(CH_2)_n-X-Y-Q'$ (in which, n is integer 0 to 5; X and Y are, independent from each other, connecting bond, alkylene group which may be substituted by hydroxyl group, cycloalkylene group , alkenylene group which may be substituted by lower alkyl group, group -NHCO- or group -CONH-; Q' is phenyl group which may be substituted, phenoxy group which may be substituted, benzoyl group which maybe substituted, pyridyl group which may be substituted, quinolyl group which may be substituted, isoquinolyl group which may be substituted; benzothiazole group which may be substituted; or benzimidazole group which may be substituted;

or pharmaceutically acceptable salts thereof.

[Claim 3] The aminophenoxyacetamide derivative of formula (I) claimed in claim 1, wherein,

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group; or alkyl group which

may be substituted;

R^5 is hydrogen atom; or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

or pharmaceutically acceptable salts thereof.

[Claim 4] The aminophenoxyacetamide derivative of formula (I) claimed in claim 1, wherein,

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group; or alkyl group which may be substituted;

R^5 is hydrogen atom; or alkyl group which may be substituted;

E^1 and E^2 are -NH-;

or pharmaceutically acceptable salts thereof.

[Claim 5] The aminophenoxyacetamide derivative of formula (I) claimed in claim 2, wherein,

R^5 is hydrogen atom; or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

when X is connecting bond, Y is -CONH-; or when X is -CONH-, Y is connecting bond;

Q is phenyl group which may be substituted;

or pharmaceutically acceptable salts thereof.

[Claim 6] The aminophenoxyacetamide derivative of formula (I) claimed in claim 2, wherein,

R^5 is hydrogen atom; or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

X and Y are, independent from each other, connecting

bounds; or alkylene group which may be substituted by hydroxyl group;

or pharmaceutically acceptable salts thereof.

[Claim 7] Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

[Claim 8] Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

[Claim 9] Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3 or 4, as an active ingredient.

[Claim 10] Medicament containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 5 or 6, as an active ingredient.

[Claim 11] Calbindin-D-28Kd, which is Ca^{2+}-binding proteins, induction agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

[Claim 12] Calbindin-D-28Kd, which is Ca^{2+}-binding proteins, induction agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

[Claim 13] Calbindin-D-28Kd, which is Ca^{2+}-binding proteins, induction agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3 or 4, as an active ingredient.

[Claim 14] Calbindin-D-28Kd, which is Ca^{2+}-binding

proteins, induction agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 5 or 6, as an active ingredient.

[Claim 15] A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

[Claim 16] A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

[Claim 17] A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3 or 4, as an active ingredient.

[Claim 18] A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 5 or 6, as an active ingredient.

[Claim 19] Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

[Claim 20] Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders

such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 2, as an active ingredient.

[Claim 21] Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 3 or 4, as an active ingredient.

[Claim 22] Medicament for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which contains aminophenoxyacetamide derivative or a pharmaceutically acceptable salt thereof according to claim 5 or 6, as an active ingredient.

[Claim 23] A method for selecting neuroprotective compound, in which said method is evaluating the activation of receptor of various kinds of physiological active substances and the phosphorylation of FGF receptor, due to the introduction of the calbindin-D-28Kd.

[Claim 24] The method for selecting neuroprotective compound according to claim 23, in which said method is

evaluating the autophosphorylation of FGF receptor.

[Claim 25] The method for selecting neuroprotective compound according to claim 23, wherein said method is performed by combining all the Test 1 to 4, by combining Test 1 and 2, by combining Test 1, 2 and 3, or by combining Test 1, 3,and 4, respectively, as following;

Test 1: Evaluation for cytoprotective effect of the compound against glutamate induced cell death,

Test 2: Evaluation for antagonism against cell death by treatment of inhibitors for FGF receptor, neurotrophin-3 (NT-3) receptor, neurotrophin-4/5 (NT-4/5) receptor, brain-derived neurotrophic factor (BDNF) receptor, insulin-like growth factor-I/II (IGF-I/II) receptor, nerve growth factor (NGF) receptor, platelet-derived growth factor (PDGF) receptor, estrogen receptor, and for antagonism against autophosphorylation of FGF receptor by treatment of MTA [5-deoxy-5-methyl-thioadenosine], to determine the cytoprotective effect is is whether neuroprotective effect through phosphorylation of receptors of various physiologically active substances and FGF receptor,

Test 3: Evaluation for Calbindin-D-28Kd inducing effect of the compound, and,

Test 4: Evaluation for cytoprotective inhibiting effect of the compound by antisense oligonucleoride of Calbindin-D-28Kd.

[Claim 26] Neuroprotevive compounds selected by the method according to any one of claims 23 to 25.

[Claim 27] Medicament containing neuroprotective compounds according to claim 26.

[Claim 28] The medicament according to claim 27 for treating or improving of cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well

as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

【Disclosure of the invention】

【0001】

【Technical field】

The present invention relates to cerebral functional or organic disorder improving and treating agents containing aminophenoxyacetamide derivatives and pharmaceutically acceptable salt thereof having neuroprotective effect by introducing calbindin-D-28Kd, one of Ca^{2+}-binding proteins, as an active ingredient, and to the methods for selecting these aminophenoxyacetamide derivatives. More specifically, the present invention relates to therapeutic and improving agents for cerebral function due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis. Furthermore, the present invention relates to therapeutic and improving agents for cerebral organic disorder such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

【0002】

【Background Art】

It is considered that the progressive delayed type cell death, observed in cerebral injury and cerebrovascular disease such as intracerebral hemorrhage, transient cerebral ischemia, and cerebral infarction, is mainly caused by increased concentration of the intracellular Ca^{2+} due to various factors related to signal transductions. Such factors related to signal transduction include, for example, the activation of glutamic acid receptor by over releasing glutamic acid which is excitability transfer factor, the activation of ion channel, and

the induction of active oxygen/free radicals. [F. B. Meyer, Brain Res. Rev., 14, 227 (1989); E. Boddeke et al., Trends Pharmacol. Sci., 10, 397 (1989); J. M. McCall et al., Ann. Rep. Med. Chem., 27, 31 (1992)].

【0003】

From these points of view, medicaments for preventing or suppressing the death of neurocyte, such as antagonists for glutamic acid receptor, calcium antagonists, antioxidants and so on have been developed. However, these clinically used medicaments suppress only few pathways related to increase of the cellular Ca^{2+} concentration, and are not sufficient for preventing or suppressing the death of neurocyte.

【0004】

On the contrary, calbindin-D-28Kd is induced by activation of many physiologically active substance's receptors such as FGF receptor, NT-3 receptor, NT-4/5, BDNF receptor, IGF-I/II receptor, NGF receptor, PDGF receptor, estrogen receptor and so on, and as well as by activation of bFGF receptor, which is one of nerve growth factor receptors [C. V.- Abejon et el., Neuron, 15, 105 (1995); A. Silva et al., Brain Res. Bull., 1, 35 (2000)]. And calbindin-D-28kd, one of Ca^{2+}-binding proteins and mainly distributed in friable site of central nervous ischemic disease, possesses buffer action against the increase of cytotoxic cellular Ca^{2+} concentration. [A. M. Lacopino et al., Neurodegeneration, 3, 1 (1994); M. P. Mattson et al., Neuron, 6, 41 (1991)]

【0005】

Accordingly, it is expected to achieve sufficient neuroprotective effects against the increase of cellular Ca^{2+} concentration caused by any kinds of pathways if cabindin-D-28Kd, one of the Ca^{2+}-binding proteins per se, can be supplied in a living body. That is, it is expected that medicaments containing

cabindin-D-28Kd would be effective therapeutic and improving agents against cerebral functional and organic disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis. It is also expected to be effective against cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

【0006】

However, because cabindin-D-28Kd is unstable high molecular protein having 28 Kd (kilo dalton) of molecular weight, it is difficult to be administered directly into central nervous site of a living body in view of pharmacological standpoint.

【0007】

On the other hand, the lower molecular compounds having effect on introduction of the calbindin-D-28Kd can be easily prepared into the various kinds of pharmaceutical compositions by the conventional technique. Therefore, these lower molecular compounds introduce the calbindin-D-28Kd after easily administered into a body, and possess buffer action against the increase of the cellular Ca^{2+} concentration. That is, these lower compounds can be effective compounds for improving and treating cerebral functional and organic disorders.

【0008】

【The problem to be solved in the Invention】

Under these circumstances, the purpose of the present invention is to select and to provide the lower molecular compounds having neuroprotective effect by introducing the calbindin-D-28Kd, one of Ca^{2+}-binding proteins, thorough phosphorylation of receptors of various physiologically active substances, as well as low toxicity in suitable preparations of pharmaceutical compositions such as intravenous injectable

solution.

【0009】

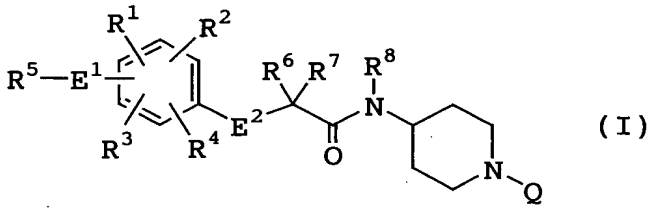
The further purpose of the present invention is to provide the therapeutic and improving agents against cerebral functional disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis, as well as cerebral organic disorders such as senile dementia, cerebral injury, cerebral operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

【0010】

【Means to solve the problem】

As one aspect of the present invention, it is provided aminophenoxyacetamide derivatives represented by the following formula (I):

【Formula 2】



(I)

【0011】

wherein,

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; hydroxy group; alkoxy group; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

E^1 is oxygen atom; sulfur atom or group $-NR^9$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl

group which may be substituted or aralkyl group which may be substituted);

E^2 is oxygen atom; sulfur atom or group $-NR^{10}$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted or aralkyl group which may be substituted);

Q is aryl group which may be substituted;

(provided that both E^1 and E^2 do not represent oxygen atom nor sulfur atom at the same time);

or pharmaceutically acceptable salts thereof.

【0012】

Furthermore, the present invention provides the aminophenoxyacetamide derivatives of the formula (I), in which;

R^1, R^2, R^3 and R^4 all are methyl group;

when E^1 is oxygen atom; E^2 is the group $-NR^9$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted or aralkyl group which may be substituted); or when E^1 is group $-NR^{10}$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted); E^2 is oxygen atom;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

Q is group $-(CH_2)_n$-X-Y-Q' (in which, n is integer 0 to 5; X and Y are, independent from each other, connecting bond, alkylene group which may be substituted by hydroxyl group, cycloalkylene group , alkenylene group which may be substituted by lower alkyl group, group -NHCO- or group -CONH-; Q' is phenyl group which may be substituted, phenoxy group which may be substituted, benzoyl group which maybe substituted, pyridyl group which may be

substituted, quinolyl group which may be substituted, isoquinolyl group which may be substituted; benzothiazole group which may be substituted or benzimidazole group which may be substituted; or pharmaceutically acceptable salts thereof.

【0013】

More specifically, the following compound groups (1) to (4) are the specific embodiments of the aminophenoxyacetamide derivatives of the formula (I) of the present invention having the excellent effect.

【0014】

(1) The aminophenoxyacetamide derivatives claimed in claim 1, wherein;

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group or alkyl group which may be substituted;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

or pharmaceutically acceptable salts thereof.

【0015】

(2) The aminophenoxyacetamide derivatives claimed in claim 1, wherein;

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group or alkyl group which may be substituted;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 and E^2 are -NH-;

or pharmaceutically acceptable salts thereof.

【0016】

(3) The aminophenoxyacetamide derivatives claimed in claim 2,

wherein;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

when X is connecting bond, Y is -CONH-; or when X is -CONH-, Y is connecting bond;

Q is phenyl group which may be substituted;

or pharmaceutically acceptable salts thereof.

【0017】

(4) The aminophenoxyacetamide derivatives claimed in claim 2, wherein;

R^5 is hydrogen atom or alkyl group which may be substituted;

E^1 is -NH-;

E^2 is oxygen atom;

X and Y are, independent from each other, connecting bounds or alkylene group which may be substituted by hydroxyl group;

or pharmaceutically acceptable salts thereof.

【0018】

According to the present inventor's investigations, it is confirmed that the aminophenoxyacetamide derivatives represented by the formula (I) effectively induced the calbindin-D-28Kd in low concentration and possessed excellent neuroprotective effect.

【0019】

Further, these compounds are also confirmed to have high safety margin, and are suitable for preparation of various kinds of pharmaceutical compositions.

【0020】

Therefore, as still a further embodiment, the present invention provides an improving and therapeutic agent for the

cerebral functional and organic disorders containing aminophenoxyacetamide derivatives represented by the formula (I) or pharmaceutically acceptable salt thereof, as an active ingredient.

【0021】

As further embodiment, the present invention provides effective and simple method of selecting (screening) lower molecular compound having effect on induction of the calbindin-D-28Kd, one of Ca^{2+}-binding proteins.

【0022】

The method of selecting low molecular compound is composed by several evaluation tests mentioned below;

(1) Evaluation test to compare the cytoprotective effect of the test compounds against glutamate induced cell death in the case of administrating the test compounds before to the case adding the glutamate simultaneously for inducing the cell injury.

(2) The test to confirm that the aforementioned cytoprotective effect is whether neuroprotective effect through phosphorylation of receptors of various physiologically active substances or not. These tests are conducted by the antagonist test suing the inhibitor of FGF receptor, NT-3 receptor, NT-4/5 receptor, BDNF receptor, IGF-I/II receptor, NGF receptor, PDGF receptor, estrogen receptor, or MTA (5-Deoxy-5-Methylthioadenosine), which specifically inhibits self phosphorylation of FGF receptor.

(3) Evaluation test of calbindin-D-28Kd inducing effect.

(4) Evaluation for cytoprotective inhibiting effect by antisense oligonucleoride of calbindin-D-28Kd.

【0023】

By the above stated evaluation tests, the following

compounds can be selected. That is;

Evaluation test (1):

This test is to evaluate whether the test compounds have cytoprotective effect against glutamate induced cell death, by administrating such testing compounds before or simultaneously along with the glutamate to induce the cell injury.

If the test compound shows greater cytoprotective effect against cell death induced by glutamate administration by pre-treatment than by simultaneously treatment, the compound may possess effect of inducing protein like substance, which shows cytoprotective effect. Therefore, the compound possessing cytoprotective effect based on inducing protein like substance, including calbindin-D-28Kd, one of Ca^{2+}-binding proteins, is selected by this evaluation test.

【0024】

Evaluation test (2):

In the case where cytoprotective effect disappears by administration of inhibitors to FGF receptor, NT-3 receptor, NT-4/5 receptor, BDNF receptor, IGF-I/II receptor, NGF receptor, PDGF receptor and estrogen receptor, then it is confirmed that such cytoprotective effect is caused by activation of these receptors. Furthermore, in the living cell, MTA (5-Deoxy-5-Methylthioadenosine) specifically inhibits autophosphorylation of FGF receptor. Disappearance of neuroprotective effect by the treatment with MTA confirms that such neuroprotective effect involves phosphorylation of FGF receptor. Therefore, this evaluation test would select the compound which neuroprotective effect is expressed by activation of receptors of various physiologically active substances and through phosphorylation of FGF receptor.

【0025】

Evaluation test (3):

The compound having effect of inducing calbindin-D-28Kd would be selected by this evaluation test.

【0026】

Evaluation test (4):

It is necessary to produce the protective protein for the signal transfer action of cells through the phosphorylation of receptors of various physiologically active substances for the cytoprotective effect of the compounds, and the calbindin-D-28Kd is one of that protective proteins. Therefore, with this evaluation test, the compound which makes neuroprotective effect disappear under blocking of calbindin-D-28Kd production by using calbindin-D-28Kd antisense is selected. That is, the compound having cytoprotective effect by producing calbindin-D-28Kd is selected.

【0027】

The present invention provides effective and simple selecting method of lower molecular compounds based on calbindin-D-28kd production increasing effect, by using all of the evaluation tests, or using the combination of evaluation tests (1) and (2), evaluation tests (1), (2) and (3), evaluation tests (1) and (3) or evaluation tests (1), (3) and (4).

【0028】

Figure 1 shows the flow chart of the selecting methods of the present invention for understanding the overview of selecting method of lower molecular compound possessing neuroprotective effect based on production increasing effect of calbindin-D-28Kd by combining aforementioned evaluation tests.

【0029】

In accordance with the selecting methods of the present invention, the compounds specifically described in the description of the present invention is selected as lower molecular compound possessing production increasing effect of

calbindin-D-28kd, one of Ca^{2+}-binding protein. However, these selecting methods can be applied to selecting various compounds possessing neuroprotective effect based on activation of physiologically active substance's receptor and calbindin-D-28kd production increasing effect involving autophosphorylation of FGF receptor, and are not limited to the selection of the compounds described in this specification.

【0030】

【BEST MODE FOR CARRYING OUT THE INVENTION】

The aminophenoxyacetamide derivatives of the present invention are further described by the following embodiments.

【0031】

The aminophenoxyacetamide derivatives of the present invention include aminophenoxyacetamides, aminoanilinoacetamides, aminothiophenoxyacetamides, oxyanilinoacetamides and thioanilino-acetamides. Therefore, "aminophenoxyacetamide derivatives" in this specification include all the derivatives stated above as long as not stated otherwise.

【0032】

In the aminophenoxyacetamide derivatives of the formula (I) provided by the present invention with reference to various substitution group of R^1 to R^{10}, "halogen atom" includes fluorine atom, chlorine atom and bromine atom.

【0033】

The term "alkoxy group" stands for a straight-chained or branched-chained C_1-C_5 alkoxy group, and may include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy and the like.

【0034】

The term "alkyl group which may be substituted" stands for a straight-chained or branched-chained C_1-C_5 alkyl group which may be halogen-substituted, and may include, for example, methyl,

ethyl, propyl, trifluoromethyl group, and the like.

【0035】

The "aryl", a part of the term "aryl group which may be substituted", stands for C_4-C_{14} aryl group containing at least one hetero atom(s) such as nitrogen and oxygen atom(s). Examples of the preferred aryl group include phenyl, pyridyl and naphthyl. The suitable substituents of said aryl group include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group having 1 to 5 carbon atoms such as methoxy group and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl.

【0036】

The "aralkyl", a part of the term "aralkyl group which may be substituted", stands for C_5-C_{12} aralkyl group containing at least one hetero ring atom(s) such as nitrogen and oxygen atom(s). The examples include benzyl, phenethyl, pyridylmethyl, and pyridylethyl.

【0037】

The suitable substituents of said aralkyl group include halogen atoms such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy group and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl.

【0038】

The "aryl", a part of the term "aryl group which may be substituted" represented as "Q", stands for C_4-C_{14} aryl group which may contain at least one hetero atom(s) such as nitrogen and oxygen atom(s). The examples include phenyl, pyridyl and

naphthyl. The suitable substituents of said aryl group include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group having 1 to 5 carbon atoms such as methoxy group and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl and trifluoromethyl.

【0039】

Furthermore, these substituents may also include a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as fluorine atom, chlorine atom and bromine atom.

【0040】

The "alkylene", a part of the term "alkylene group which may be substituted by hydroxyl group", refers to the substituets "X" and "Y", and preferably represents a straight-chained or branched-chained C_1-C_6 alkylene group such as methylene, methylmethylene, ethylene, trimethylene, tetramethylene, cyclopropylmethylene and the like.

【0041】

The term "cycloalkylene" preferably stands for C_3-C_6 cycloalkylene and may include 1,1-cyclopropylene, 1,2-cyclopropylene, 1,1-cyclobutylene, 1,1-cyclopentylene, 1,1-cyclohexylene and the like. Among them, 1,1-cyclopropylene and 1,2-cyclopropylene are more preferable.

【0042】

The "alkenylene", a part of the term "alkenylene group which may be substituted by lower alkyl group", may include C_2-C_4 alkenylene such as vinylene, and butadiene, and vinylene is preferably used. The lower alkyl group, which is substituent of alkenylene group, may be methyl, ethyl, propyl, isopropyl and the like.

【0043】

The term "connected bond" with reference to "X" and "Y" means direct bond. Therefore, if "X" and/or "Y" are connected bond, two adjacent substituents of "X" and/or "Y" are connected directly, and these substituents do not exist as "X" and/or "Y".

【0044】

The suitable substituents represented as "Q'" for "phenyl group which may be substituted", "phenoxy group which may be substituted", "benzoyl group which may be substituted", "pyridyl group which may be substituted", "quinolyl group which may be substituted", "isoquinolyl group which may be substituted", "benzothiazole group which may be substituted" and "benzimidazolyl group which may be substituted", may include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy, ethoxy group and so on. Furthermore, these substituents may also include a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as methyl, ethyl, trifluoromethyl and the like.

【0045】

It is understood that when the aminophenoxyacetamide derivatives of the formula (I) of the present invention exist in the isomer forms, each isomers *per se*, as well as the isomeric mixture, shall be included in the compounds of the present invention.

【0046】

Namely, the structural isomers may exist due to the substituents on the benzene ring. Furthermore, optical isomers may exist due to the asymmetric carbon atom of the hydroxy substituted "X" or "Y" of alkylene group. These isomers shall be included within the scope of the compounds of the present invention.

【0047】

The aminophenoxyacetamide derivatives of the formula (I) include the compounds (Ia), (Ib) (Ic) and (Id) obtained by the synthetic process mentioned latter. For example, these compounds may be prepared by the following.

【0048】

The compound (IV), obtained by the reaction of the compound (II) with the ester derivative (III), is hydrolyzed to convert into the carboxylic acid derivative (V). Furthermore, the compound (VIII) is obtained by the reaction of the amine derivative (VI) with the compound (VII), and the protecting group of the compound (VIII) is removed to obtain the amine derivative (IX). Then, the obtained compound (V) is converted into amide compound (VII) by the condensation reaction with the compound (IX). Further, the protecting group in the compound (IX) thus obtained is removed to obtain compound (Ia), the compound of formula (I) in the Claim 1 of the present invention (Process 1).

【0049】

The compound (Ib), the aminophenoxyacetamide derivative of formula (I) in the Claim 2 of the present invention, can be obtained by the following. The amide compound (XII) is obtained by condensation reaction of the carboxylic acid derivative (V'), which is obtained in the Process 1, with compound (XI), and the protecting group of the resultant was removed (Process 2).

【0050】

The compound (Ib), obtained in the Process 2, can be converted to the compound (Ic) by the reaction with the compound (XIII) (Process 3).

【0051】

Furthermore, the compound (Id) can be obtained by reacting the compound (Ib) with the compound (XIV) (Process 4).

Each process will be further illustrated by the following

reaction scheme.

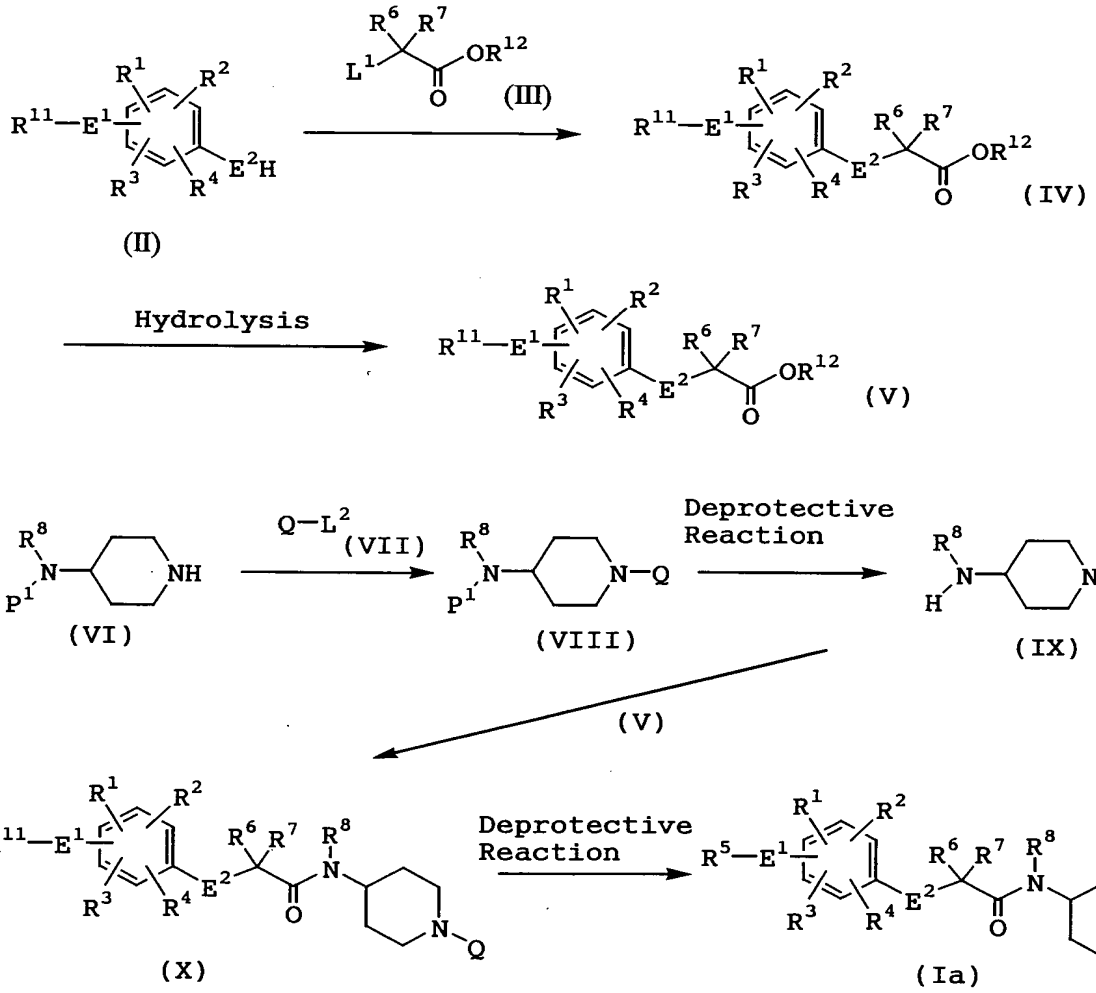
【0052】

Process 1:

According to this process 1, the compound (Ia) can be obtained from the known starting compound (II).

【0053】

【Formula 3】



【0054】

wherein, R^1 to R^8, E^1 and E^2 have the same definitions as above; Q has the same meaning as defined in claim 1; and R^{11} is alkyl group which may be substituted, aryl group which may be substituted; aralkyl group which may be substituted; tert-butoxycarbonyl

group; ethoxycarbonyl group; acetyl group; benzyloxycarbonyl group; p-methoxybenzyloxycarbonyl group; R^{12} is a straight-chained or branched-chained C_1-C_5 alkyl group; L^1 is leaving group which can easily be replaced with amino, hydroxy and mercapto group; L^2 is leaving group which can be easily replaced with amino, and boric acid; P^1 is tert-butoxycarbonyl group, ethoxycarbonyl group, acetyl group, benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, benzyl group or trifluoroacetyl group.

【0055】

in the first step, the compound (II) is reacted with ester compound (III) to derive the compound (IV).

【0056】

Namely, for the first step, the compound (II) is reacted with 1.0 to 1.5 mole equivalent of ester compound (III) in the inert solvent such as benzene, toluene, tetrahydrofuran, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, acetone, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol, diethyl ether and the like, and if necessary in the presence of the base such as triethylamine, diisopropylethylamine, pyridine and the like, or an inorganic base such as sodium, sodium hydride, potassium, potassium hydride, sodium methoxide, potassium, tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, sodium bicarbonate, potassium bicarbonate and the like, under stirring at -20° C to 150° C, preferably at 0° C to 100° C.

【0057】

These organic base and inorganic base may be used in combination, and sodium iodide, potassium iodide or tetrabutylammonium iodide can be added in the reaction mixture.

【0058】

The substituent "L^1" in the ester derivative (III) may be the leaving group which can easily be replaced with amino,

hydroxy or mercapto group, and examples include halogen atom such as chlorine atom, bromine atom, iodide atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group, 3-nitrobenzenesulfonyloxy group and the like.

【0059】

The compound (II) and compound (III) to be used in this reaction can be commercially available and known compounds, or can be easily prepared from known compounds by using common methods.

【0060】

Examples of the compound (II) include 4-(tert-butoxycarbonylamino)phenol, 4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenol, 2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylphenol, 3-(tert-butoxycarbonylamino)-2,4,5,6-tetramethylphenol, 4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenol, 4-(tert-butoxycarbonylamino)-2-chloro-3,5,6-trimethylphenol, 4-(tert-butoxycarbonylamino)-2,3,6-trimethylphenol, 4-(tert-butoxycarbonylamino)-2,3-dimethylphenol, 4-(tert-butoxycarbonylamino)-2,5-dimethylphenol, 2-(tert-butoxycarbonylamino)-4,6-dimethylphenol, 5-(tert-butoxycarbonyl-amino)-2-methoxyphenol, 5-(tert-butoxycarbonylamino)-4-chloro-2-metoxyphenol, 4-(tert-butoxycarbonylamino)-2,6-dichlorophenol, 4-(tert-butoxycarbonylamino)-2,3,4,6-tetramethylaniline, 4-metoxy-2-methylaniline, 4-(tert-butoxycarbonylamino)-2,5-dimethylaniline, 2-(tert-butoxycarbonylamino)-4,5-dimethylaniline, 3-(tert-butoxycarbonylamino)-2,4,6-trimethylaniline, 2-(tert-butoxycarbonylamino)-4,5-dimethylaniline, 4-(tert-butoxycarbonylamino)-2,5-dichloroaniline, 4-(tert-butoxycarbonylamino)-2,6-dichloroaniline, 2-(tert-butoxy carbonylamino)-4,5-dichloroaniline, 4-(tert-butoxycarbonylamino)-2-methoxy-5-methylaniline, 4-(tert-butoxycarbonylamino)-2,5-dimethoxyaniline, 4-(benzyloxycarbonylamino)phenol, 4-(benzyl-

oxycarbonylamino)-2,3,5,6-tetramethylphenol, 2-(benzyloxycarbonylamino)-3,4,5,6-tetramethylphenol, 3-(benzyloxycarbonylamino)-2,4,5,6-tetramethylphenol, 4-(benzyloxycarbonylamino)-2,3,5-trimethylphenol, 4-(benzyloxycarbonylamino)-2-chloro-3,5,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3-dimethylphenol, 4-(benzyloxycarbonylamino)-2,5-dimethylphenol, 2-(benzyloxycarbonylamino)-4,6-dimethylphenol, 5-(benzyloxycarbonylamino)-2-methoxyphenol, 5-(benzyloxycarbonylamino)-4-chloro-2-methoxyphenol, 4-(benzyloxycarbonylamino)-2,6-dichlorophenol, 4-(benzyloxycarbonylamino)-2,3,4,6-tetramethylaniline, 4-methoxy-2-methylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethylaniline, 2-(benzyloxycarbonylamino)-4,5-dimethylaniline, 3-(benzyloxycarbonylamino)-2,4,6-trimethylaniline, 2-(benzyloxycarbonylamino)-4,5-dimethylaniline, 4-(benzyloxycarbonylamino)-2,5-dichloroaniline, 4-(benzyloxycarbonylamino)-2,6-dichloroaniline, 2-(benzyloxycarbonylamino)-4,5-dichloroaniline, 4-(benzyloxycarbonylamino)-2-methoxy-5-methylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethoxyaniline and so on.

【0061】

The ester compound of the formula (III) includes, for example, ethyl bromoacetate, ethyl 2-bromopropionate, ethyl 2-bromo-2-methylpropionate, and so on.

【0062】

Then, the obtained compound (IV) is hydrogenated to convert into carboxylic acid derivative (V) by the common methods.

【0063】

The compound (IX) to be used for the condensation reaction with the above-obtained carboxylic acid derivative (V) can be obtained by the following manner.

【0064】

In the first step, the amine derivative (VI) is conducted

by the condensation reaction with the compound (VII) to obtain the compound (VIII).

【0065】

Namely, for the first step, the amine derivative (VI) is conducted by the condensation reaction with the compound (VII) in the inert solvent such as benzene, toluene, xylene, diethylaniline, tetrahydrofuran, diethylether, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, methanol, ethanol, propane-2-ol, butyl alcohol and the like, and if necessary in the presence of the base such as triethylamine, diisopropylamine, and the like, or an inorganic base such as sodium hydride, potassium hydride, sodium tert-butoxide, potassium, tert-butoxide, sodium ethoxide, sodium carbonate, sodium bicarbonate, cesium carbonate and the like, under stirring at the room temperature to 180°C, to obtain the compound (VIII).

【0066】

The reaction of the amine compound (VI) with the compound (VII) can also be conducted in the inert solvent such as benzene, toluene, xylene and diethylaniline, and in the presence of palladium catalyst such as tris(dibenzylidene-acetone)dipalladium, diacetoxypalladium, palladium chloride and the like, phosphine coordination compound such as tir-n-butylphosphine, tir-tert-butylphosphine, tri-o-tolylphosphine, BINAP and the like, and the base such as sodium tert-butoxide and cesium carbonate under stirring at 50°C to 150°C.

【0067】

Furthermore, the reaction of the compound (VII), in which the substitute "L^2" is boric acid residue, with the amine compound (VI) can be conducted in the inert solvent, and in the presence of the base and 1.0 to 2.0 mole equivalent of copper acetate ($CuOAc_2$), under stirring at the room temperature to 100°C [D. M. T. Chan et al., Tetrahedron Letters, 39, 2933 (1998)]. The inert

solvent to be used in this reaction may be dichloromethane, chloroform and the like, and the base may be triethylamine, pyridine and the like.

【0068】

The compound (VI) to be used for the reaction with the compound (VII) is known compound [cf. R. H. Mach et al., J. Med. Chem., 36, 3707 (1993)], or can be easily prepared by the methods described in EP 0184257 A1 [R. A. Stokbroekx, et al.].

【0069】

Then, the protecting group at nitrogen atom of the compound (VIII) thus obtained is removed to obtained the amine derivative (IX).

【0070】

This reaction may vary depend on the protecting group on the nitrogen atom of the compound (VIII). For example, the compound (VIII) is treated with acids such as acetic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethane-sulfonic acid, hydrochloric acid, sulfuric acid, or nitric acid in an inert solvent such as benzene, toluene, acetonitrile, tetrahydrofuran, dioxane, dichloromethane, chloroform, carbon tetrachloride, water, methanol, ethanol, and the like.

【0071】

Furthermore, the removal of the protecting group may also be carried out by hydorgenolysis of the compound (VIII) using hydrogen under 1 to 5 atmospheric pressure, in the presence of a catalyst such as palladium-carbon, palladium hydroxide, platinum, or platinum oxide, in an inert solvent such as methanol, ethanol, isopropyl alcohol, ethyl acetate or acetic acid.

【0072】

Then, the carboxylic acid derivative of the formula (V) is converted into amide derivative (X) by reaction with the compound (IX).

【0073】

The reaction conditions of this amidation reaction may vary according to the methods described in "Compendium for Organic Synthesis" (wiley-Interscience: A Division of John Wiley & Sons Ltd.).

【0074】

For example, the compound (V) is treated, optionally in the presence of an organic or an inorganic base, with diethyl cyanophosphonate (DEPC), diphenylphosphoryl azide (DPPA), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(dimethylamino-propyl)carbodiimide hydrochloride salt or 2-iodo-1-methyl-pyridinium iodide, and then reacted with compound (IX) to obtain the amide compound (X). Furthermore, the compound (V) is converted into the activated ester compound such as acid halide, symmetric acid anhydride, or mixture acid anhydride, and then, reacted with the compound (IX) to obtain the amide compound (X).

【0075】

The compound (X) thus obtained is converted into the aminophenoxyacetamide derivatives of the formula (Ia), the compound of the present invention, by the removal reaction of the protecting group on the nitrogen atom of the amide compound (X).

【0076】

Although each compounds obtained in the above process 1 may be used for the next reaction without further purification, it can also be used after further purification if necessary in conventional manner such as recrystallization or column chromatography and so on.

【0077】

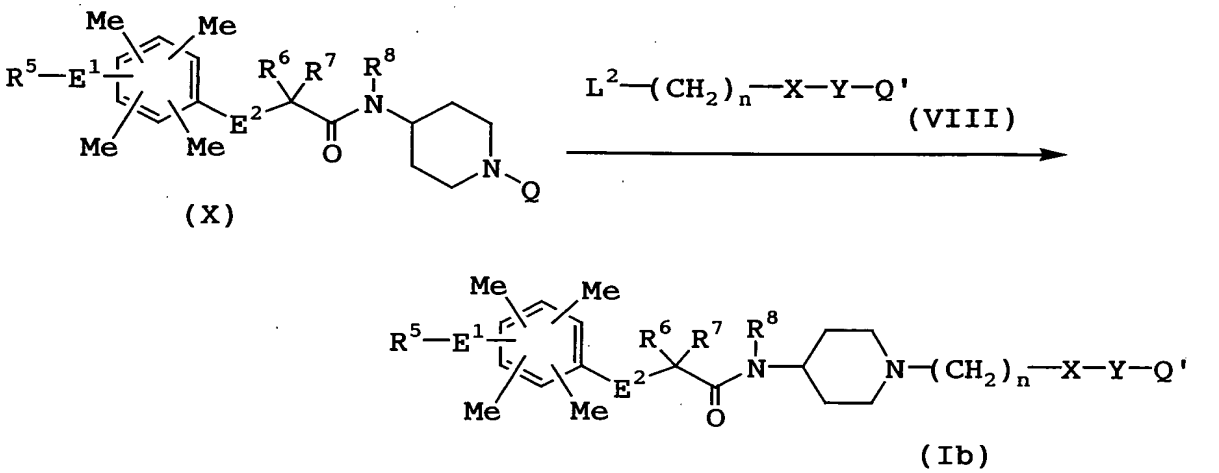
Process 2:

According to this process 2, the aminophenoxyacetamide derivative of the formula (Ib) can be synthesized from the compound (V') [wherein, R^1 to R^4 are methyl groups, E^1 is oxygen

atom and E^2 is $-NR^9$; or E^1 is $-NR^{10}$ and E^2 is oxygen atom] obtained in the process 1 mentioned above.

【0078】

【Formula 4】



【0079】

wherein, R^5 to R^8 and R^{11} have the same definitions as above, E^1 and E^2 have the same meanings as defined in claim 2, and P^2 is tert-butoxycarbonyl group, ethoxycarbonyl group, acetyl group, benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, benzyl group or trifluoroacetyl group.

【0080】

Namely, the compound (V') [wherein, R^1 to R^4 are methyl groups, E^1 is oxygen atom and E^2 is $-NR^9$; or E^1 is $-NR^{10}$ and E^2 is oxygen atom] is reacted with the compound (XI) to obtain the amide compound (XII), and then, the protecting group of the resultant compound (XII) is removed off to give the aminophenoxyacetamide derivative (Ib).

This reaction may be carried out by the same manner as described in the Process 1.

【0081】

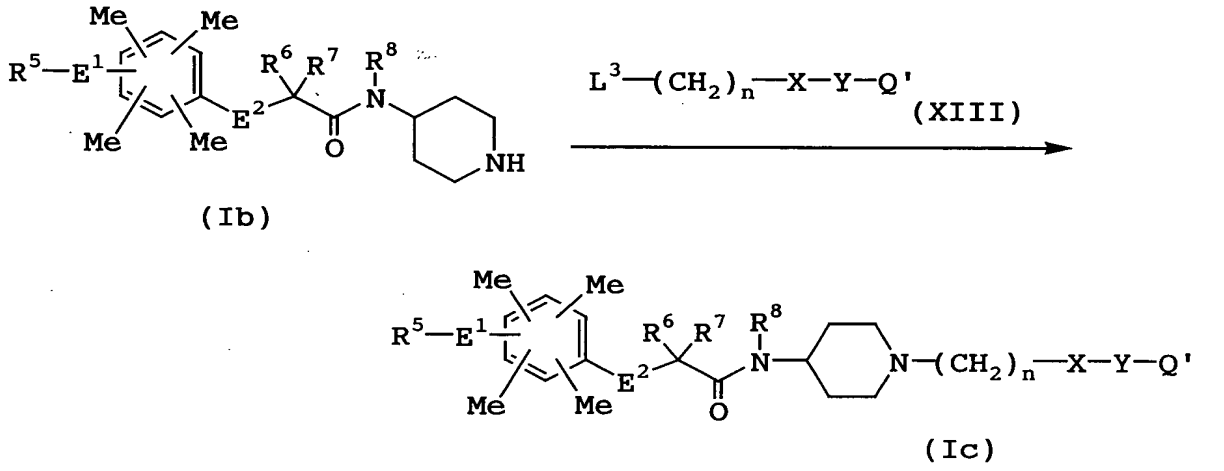
Process 3:

In the process 3, the aminophenoxyacetamide derivative of

the formula (Ic) can be derived from reacting the compound (XIII) with the resultant of the formula (Ib) obtained in the process 2 mentioned above.

【0082】

【Formula 5】



【0083】

wherein, R^5 to R^8 and have the same definitions as above, n, X, Y, Q', E^1 and E^2 have the same meanings as defined in claim 2.

【0084】

According to this process 3, the aminophenoxyacetamide derivative of the formula (Ic) can be obtained from the compound (Ib) by reacting with the compound (XIII).

【0085】

Namely, the compound (Ib) is reacted with 1.0 to 1.5 mole equivalent of the compound (XIII) in the inert solvent such as benzene, toluene, tetrahydrofuran, dioxan, dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone, ether, dichloromethane, chloroform and carbon tetrachloride in the presence of the base such as triethylamine, diisopropylethylamine, pyridine and the like, or an inorganic base such as sodium, sodium hydride, potassium, potassium hydride, sodium ethoxide, sodium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate,

cesium fluoride, sodium bicarbonate, potassium bicarbonate and the like, at -50°C to 120°C, preferably at -20°C to 80°C.

【0086】

In the above reaction, Sodium iodide, potassium iodide or tetrabutylammonium iodide can be added.

【0087】

The substituent "L^3" in the compound (XIII) is the leaving group, which can easily be replaced by amino group, and examples include halogen atom such as chlorine atom, bromine atom, iodine atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group and the like.

【0088】

In this process 3, the aminophenoxyacetamide derivative of the formula (Ic) can be produced as well.

【0089】

Process 4:

In the process 4, the aminophenoxyacetamide derivative of the formula (Id) of the present invention can be obtained from the reaction of the compound (Ib), obtained in the process 2 mentioned above, with the compound (XIVa) or the compound (XIVb).

【0090】

【Formula 6】

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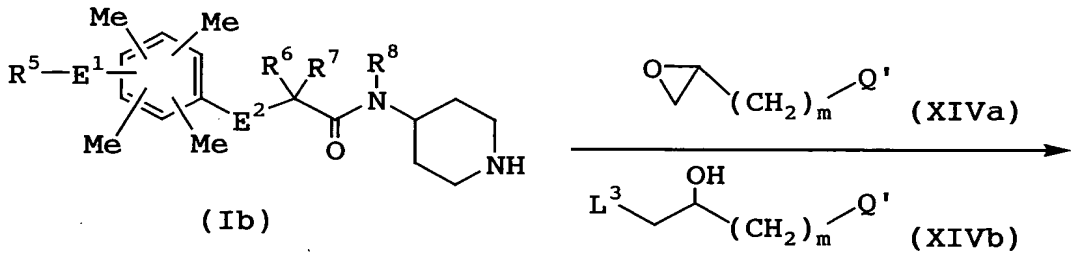
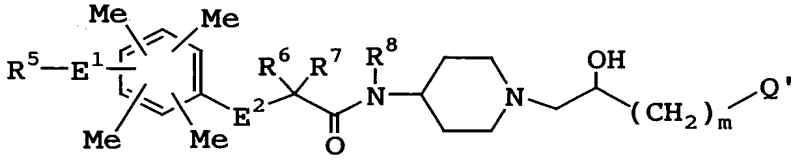


(Ib) (XIVa) (XIVb)



(Id)

【0091】

wherein, R^5 to R^8 and L^3 have the same definitions as previously mentioned, Q', E^1 and E^2 are the same meanings as defined in the claim 2, and m is integer 0 to 3.

【0092】

According to this process 4, the aminophenoxyacetamide derivative of the formula (Id) of the present invention can be obtained from the reaction of the compound (Ib), obtained in the process 2 mentioned above, with the compound (XIVa) or the compound (XIVb). For example, the compound (Ib) is reacted with 0.9 to 1.5 mole equivalent of the compound (XIVa) or (XIVb) in an inert solvent such as benzene, toluene, tetrahydrofuran, diethyl ether, ethylene glycol diethyl ether, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol and the like at from room temperature to about 200 °C, preferably at about 50°C to about 150°C, to produce the aminophenoxyacetamide of the formula (Id).

【0093】

Examples of the compound (XIVa) include epibromohydrin, epichlorohydrin, (R)-epichlorohydrin, (S)-epichlorohydrin and the

like, and examples of the compound (XIVb) include glycidyl tosylate, (R)-glycidyl tosylate, (S)-glycidyl tosylate, (R)-glycidyl 3-nitro-benzensulfonate, (S)-glycidyl 3-nitrobenzesulfonate, (R)-glycidyl 4-nitro-benzoate, (S)-glycidyl 4-nitrobenzoate, gylcidyltrimethylammonium chloride and the like.

【0094】

In this process 4, the aminophenoxyacetamide derivative of the formula (Id) can be produced as well.

【0095】

The aminophenoxyacetamide derivatives of the formula (I) thus obtained may be isolated and purified in conventional manner, such as recrystallization, column chromatography and the like.

【0096】

The following are aminophenoxyacetamide derivatives of the formula (I) of the present invention obtained by the above-mentioned methods.

【0097】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclopropyl-methyl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methyacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-

piperidinyl]acetamide,

【0098】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylacetamide, 3-{4-[[2-(4-amino-2,3,5,6-tetramethylphenoxy)acetyl](methyl)amino]piperidino}-2-phenylpropionic acid, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]acetamide,

【0099】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}acetamide, 2-(4-amino-

2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-(1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl)acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-piperidinyl]acetamide,

【0100】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylpropamide, 2-(4-amino,2,3,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}popanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylpropanamide,

【0101】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-

piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphtylmethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 3-{4-[[2-(4-amino-2,3,5,6-tetramethylphenoxy)propanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid,

【0102】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide,

【0103】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(4-

amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-peperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N,2-dimethylpropanamide,

【0104】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxyethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-pyridinylmetyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylsulfonyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-

N,2-dimethyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]propanamide,

【0105】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenacyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]propanamide, 3-{4-[[2-(4-amino-2,3,5,6-tetramethylphenoxy)-2-methylpropanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(1-phenylcyclopropy)methyl-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylacety)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-phenylpropyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N,2-dimethylpropanamide,

【0106】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-

N,2-dimethyl-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide,

【0107】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyridinyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methyacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylacetamide,

【0108】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]acetamide, 2-(2-amino-

3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylacetamide, 3-{4-[[2-(2-amino-3,4,5,6-tetramethylphenoxy)acetyl](methyl)amino]piperidino}-2-phenylpropionic acid, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylacetamide,

【0109】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylacetamide,

【0110】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-(1-{2-oxo-2-

[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl)acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6,-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylprppamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methylpropanamide,

【0111】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}popanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphtylmethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-

tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]propanamide,

【0112】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 3-{4-[[2-(2-amino-3,4,5,6-tetramethylphenoxy)propanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide,

【0113】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide,

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-

piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]propanamide,

【0114】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-peperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxyethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-pyridinylmetyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide,

【0115】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylsulfonyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-

(phenacyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]propanamide, 3-{4-[[2-(2-amino-3,4,5,6-tetramethylphenoxy)-2-methylpropanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(1-phenylcyclopropy)methyl-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylacety)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide,

【0116】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-phenlypropyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenyl)-4-piperidinyl]propanamide,

【0117】

2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyridinyl)-4-peperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyrimidinyl)-4-pirepeidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexymethyl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methyacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylacetamide,

【0118】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylacetamide, 3-

{4-[[2-(3-amino-2,4,5,6-tetramethylphenoxy)acetyl](methyl)amino]piperidino}-2-phenylpropionic acid,

【0119】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]acetamide,

【0120】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-(1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl)acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-

piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]acetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N-methylpropanamide,

【0121】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N-methylpropamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxyethyl)-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-pyridinylmethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-naphtylmethyl)-4-piperidinyl]propanamide,

【0122】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenacyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 3-{4-[[2-(3-amino-2,4,5,6-

tetramethylphenoxy)propanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenylacetyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-phenylpropyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N-methylpropanamide,

【0123】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(phenyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N-methylpropanamide,

【0124】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyridinyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cyclohexylmethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-butyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-acetyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(morpholinyl)ethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxyethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzyl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-benzoyl-4-piperidinyl]-N,2-dimethylpropanamide,

【0125】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-pyridinylmetyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2,3,4-trimethoxybenzyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylsulfonyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-naphthylmethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-quinolinylmethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenacyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]propanamide, 3-{4-[[2-(3-amino-2,4,5,6-tetramethylphenoxy)-2-methylpropanoyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid, 2-(3-amino-2,4,5,6-

tetramethylphenoxy)-N,2-dimethyl-N-[1-(1-phenylcyclopropyl)methyl-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-1-methyl-2-phenylethyl)-4-piperidinyl]propanamide,

【0126】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenylacety)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-thienylacetyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-phenylpropyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(cinnamyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[(2-phenylcyclopropyl)methyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(phenylsulfonyl)ethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-phenoxyethyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(3-oxo-3-phenylpropyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-{1-[2-(methylanilino)-2-oxoethyl]-4-piperidinyl}propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]propanamide,

【0127】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-{2-oxo-2-[(1-phenylcyclopropyl)amino]ethyl}-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(phenyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,3-benzothiazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(benzimidazol-2-yl)-4-piperidinyl]-N,2-dimethylpropanamide,

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyridinyl)-4-peperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylacetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylpropanamide,

【0128】

2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-peperidinyl]acetamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanamide, 2-(4-amino-2,3,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanaminde, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylacetamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylpropanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N,2-dimethylpropanamide,

【0129】

2-(3-amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-peperidinyl]acetamide, 2-(3-amino-2,4,5,6-

tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanamide, 2-(3-amino-2,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanaminde, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(2-anilino-2-oxoethyl)-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylacetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N-methylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-[1-(1,1'-biphenyl)-4-yl-4-piperidinyl]-N,2-dimethylpropanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-peperidinyl]acetamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanamide, 2-(2-amino-3,4,5,6-tetramethylphenoxy)-N,2-dimethyl-N-[1-(4-phenoxyphenyl)-4-piperidinyl]propanaminde.

【0130】

Further, each isomers contained in the compounds of the formula (I) of the present invention can be obtained by resolution of the isomeric mixture of these compounds by the conventional methods, such as recrystallization, column chromatography, HPLC, and the like, or by using optically active reagents.

【0131】

The aminophenoxyacetamide derivatives of the present invention represented by the formula (I) may be used in the form of free bases or suitable pharmaceutically acceptable acid addition salts thereof. The pharmaceutically acceptable salts can be obtained by treating the compound (I) with an inorganic acid or an organic acid in suitable organic solvent such as ether,

tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, methanol, isopropanol, ethanol and the like.

【0132】

Examples of the inorganic acid include hydrochloric acid, sulfuric acid, hydrobromic acid, phosphoric acid, periodic acid and the like. Further, examples of the organic acid include formic acid, acetic acid, butyric acid, oxalic acid, malonic acid, propionic acid, valeric acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid and the like.

【0133】

The aminophenoxyacetamide derivatives of the present invention represented by the formula (I) or pharmaceutically acceptable salts thereof shows low toxicity and may be administered per se. However, it may be converted in the form of pharmaceutically acceptable composition with the conventional pharmaceutically acceptable carriers for improvement or treatment of various kinds of diseases due to cerebral functional or organic disorder.

【0134】

The dosage forms may include oral formulations such as capsules, tablets or parenteral formulations such as injection solution containing the compound of the formula (I) *per se*, or using the conventional excipients. For example, the capsules can be prepared by mixing the compound of the formula (I) in powder form with a suitable excipient such as lactose, starch or derivatives thereof or cellulose derivatives, and then filled in gelatin capsules.

【0135】

Also, the tablets can be prepared by mixing the active ingredients with the above-mentioned excipients, binders such as sodium carboxymethylcellulose, alginic acid or gum arabic and

water, then if necessary, making the resultant mixture into granules. Then, it may be further mixed with lubricant such as talc or stearic acid, and compressed into tablet by mean of common tableting machine.

【0136】

Injectable formulations for parenteral route also can be prepared by dissolving the compound of the formula (I) or salts thereof in sterile distilled solution or sterile physiological saline solution with solution adjuvant, and filling it into ample. A stabilizer or buffer can be used in the injectable solution, and the injectable formulation may be administered intravenously or by dripping.

【0137】

In administration of the compound of the formula (I), which possess neurocytic protecting effect by induction of calbindin-D-28Kd, one of Ca^{2+}-bindind proteins, the therapeutically effective dosage for improving cerebral functional and organic disorders is not particularly limited and may vary depending on the various kinds of factors. These factors may be the patient's condition, the severity of the disease, age, existence of a complication, administration route, formulation, as well as number of times for administration.

【0138】

A usual recommended daily dose for oral administration is within the range of 0.1-1,000 mg/day/person, preferably 1-500 mg/day/person, while a usual recommended daily dose for parenteral administration is within the range of 1/100 to 1/2 based on dose of the oral administration. These doses also may vary depending on age, as well as the patient's condition.

【0139】

【Examples】

The present invention is illustrated in more detail by way

of the following examples, but it is to be noted that the present invention is not limited by these Examples in any way.

The compound numbers in the following examples are identical to those of the Table's mentioned later.

【0140】

Example 1: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (1)

A solution of 457 mg of 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylphenoxy]acetic acid, 363 mg of 1-(tert-butoxycarbonylamino)-4-methyl-methylaminopiperidine, 2.16 g of 25% propane-phosphonic acid cyclic anhydride in acetic acid solution and 985 μl of triethylamine in 5 ml of dimethylformamide was stirred over night under room temperature. After the reaction, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture and the mixture was extracted with dichloromethane. The extract was washed with saline, dried and concentrated under reduced pressure to give the residue. The obtained residue was dissolved in 8 ml of dichloromethane, and to this solution was added 2 ml of trifluoroacetic acid under ice-cooling, then the mixture was stirred for 1 hour at the room temperature. After removal of the solvent, the resultant residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.) column chromatography (dichloromethane : methanol = 30:1) to give 192 mg (42%) of the above-mentioned compound (1).

【0141】

Example 2: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-(4-piperidinyl)propanamide (2)

The title compound (2) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]propionic acid and 1-(tert-butoxycarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

【0142】

Example 3: 2-(4-Amino-2,3,5,6-tetramethylphenoxy)-2-methyl-N-methyl-N-(4-piperidinyl)propanamide (3)

The title compound (3) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]-2-methyl propionic acid and 1-(tert-butoxycarbonylamino)-4-methylamino-piperidine by the same manner as the Example 1.

【0143】

Example 4: 2-(2-Amino-3,4,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (4)

The title compound (4) was obtained from 2-[2-(tert-butoxycarbonylamino)-3,4,5,6-tetramethylanilino]acetic acid and 1-(tert-butoxylcarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

【0144】

Example 5: 2-(3-Amino-2,4,5,6-tetramethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (5)

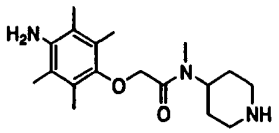
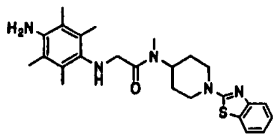
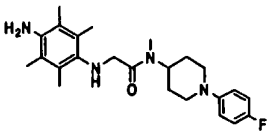
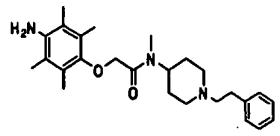
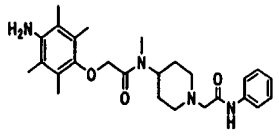
The title compound (5) was obtained from 2-[3-(tert-butoxycarbonylamino)-2,4,5,6-tetramethylanilino]acetic acid and 1-(tert-butoxycarbonylamino)-4-methylaminopiperidine by the same manner as the Example 1.

【0145】

The physiochemical datum of the compounds obtained by the above-mentioned examples is summarized in the following table 1.

【0146】

【Table 1】

No.	Chemical Structure	Properties	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
1		White Powdery Substance	(CHCl3) 2950, 2399, 1734, 1652, 1558, 1472, 1418, 1319, 1083	1.53-1.85(4H, m), 2.08(3H, s), 2.09(3H, s), 2.23(3H, s), 2.24(3H, s), 2.63(1H, m), 2.76(1H, m), 2.88&2.92(3H, each s), 3.15(2H, m), 3.48(2H, brs), 3.73&4.63(1H, each m), 4.31&4.36(2H, each s)
2		White Powdery Substance (HCl salt) (Et_2O/EtOH) 190-194℃	(HCl salt) 3424, 2929, 1624, 1540, 1468, 1412, 1262, 1126, 1095, 1018, 762	(HCl salt);DMSO 1.65-1.87 (4H, m), 2.17 (6H, s), 2.22 (3H, s), 2.24 (3H, s), 2.77 & 2.80 (3H, each s), 3.30 (2H, m), 3.96 (2H, s), 4.13 (2H, m), 4.59 (1H, m), 7.10 (1H, dd), 7.30 (1H, dd), 7.47 (1H, d), 7.78 (1H, d)
3		Pale Yellow Foamy Substance (HCl salt) (Et_2O/EtOH) 231-235℃	(HCl salt) 3420, 1651, 1511, 1451, 1407, 1237, 1166, 1101, 1012, 844	1.67-2.04 (4H, m), 2.13 (6H, s), 2.29 (6H, s), 2.65 & 2.82 (2H, each m), 2.77 & 2.92 (3H, each s), 3.46 (2H, m), 3.61 & 3.66 (2H, each s), 4.70 (1H, m), 6.88-6.98 (4H, m)
4		White Powdery Substance (HCl salt) (Et_2O/EtOH) 261-263℃	(HCl salt) 3432, 2926, 2345, 1646, 1534, 1478, 1455, 1304, 1248, 1098	1.56-2.29(6H, m), 2.09(6H, s), 2.23(3H, s), 2.24(3H, s), 2.61(2H, m) 2.75-2.85(2H, m), 2.88&2.92(3H, each s), 3.09(2H, m), 3.47(2H, brs 3.69&4.58(1H, each m), 4.32&4.35(2H, each s), 7.20(3H, m), 7.24-7.33(2H, m)
5		White Powdery Substance (HCl salt) (Et_2O/EtOH) 196-200℃	(HCl salt) 3425, 2950, 1692, 1636, 1556, 1498, 1447, 1314, 1248, 1097	1.68-2.04(4H, m), 2.09(6H, s), 2.23(6H, s), 2.29-2.55(2H, m), 2.94&2.96(3H, each s), 3.00(2H, m), 3.14&3.16(2H, each s), 3.49(2H, brs), 3.81&4.57(1H, each m), 4.33&4.36(2H, each s), 7.12(1H, m), 7.35(2H, m), 7.57(2H, d), 8.96&9.06(1H, each brs)

【0147】

The effect of aminophenoxyacetamide derivatives of the present invention represented by the formula (I) was evaluated by the following biological testing methods.

【0148】

Test 1: Evaluation for cytoprotective effect against glutamate induced cell death, by comparing the previous administration of the test compound to the glutamate administration and the simultaneous administration of the test compound along with the glutamate compound.

Test 2: Evaluation for antagonism against cell death by treatment of various kinds of receptor inhibitor and MTA [5-deoxy-5-methyl-thioadenosine].

Test 3: Evaluation for Calbindin-D-28Kd production increasing effect.

Test 4: Evaluation for cytoprotective inhibiting effect by antisense oligonucleoride.

Test 5: Evaluation for cerebral edema suppressing effect.

【0149】

By using of the above-mentioned biological tests, the selection of the compounds having neuroprotective effect by activating the receptor of various kinds of physiological active substances and autophosphorylation of FGF receptor, due to the introduction of the calbindin-D-28Kd, one of Ca^{2+}-binding proteins, was performed by combining all the Test 1 to 4, by combining Test 1 and 2, by combining Test 1, 2 and 3, or by combining Test 1, 3,and 4, respectively.

The following are the detailed description of the test methods.

【0150】

Biological test 1: Evaluation for cytoprotective effect against glutamate induced cell death

In accordance with the method of M. P. Mattson [M. P. Mattson, *Brain Res. Rev.*, 13, 179 (1988)], brain of 18-days fetus rat of Wistar strain was taken out. Then, cells of cerebral cortex (4 x 10^5 cells / ml) were seeded on poly-L-lysine coated 96 wells flat bottom plate (Sumitomo Bakelite Co., Ltd.) in concentration of 4 x 10^4 cells / each wells. In the case of the previously administration of the test compounds, 1 μM of test compounds were added after 48 hours of incubation, and 1 mM of glutamic acid were further added after 72 hours of incubation for inducing the cell injury. In the case of the simultaneously administration of the test compound, both of 1 μM of test compounds and 1 mM of glutamic acid were added after 48 hours of incubation, and further 12 hours after adding of glutamic acid, MTT [3-(4,5-dimethylthiazol-2,5-diphenyl)tetrazolium bromide] was added, and incubated for 6 hours. After incubation, dimethy sulfoxide was added to each wells, and the amounts of reduced MTT were colorimetrically analyzed by Micro ELISA Reader using 570 nm of main-wavelength and 650 nm of sub-wavelength.

【0151】

The effect of the test compounds was determined as the survival rate of living cells (%) according to the following equation:

Survival rate of living cells (%) =

[(test compound group - glutamic acid treated group) ÷ (control group - glutamic acid treated group)] x 100

That is, the survival rate of living cells after incubation of the control group was converted to 100 %, and the survival rate of living cells of the tested compounds was calculated.

【0152】

Biological test 2: Evaluation for antagonism against cell death by treatment of various kinds of receptor inhibitor of physio-

logical active substances and MTA

This biological test is performed to determine whether the cytoprotective effect of the test compounds is due to the activation of receptors of physiological active substances or not, by using antagonistic test for neutralizing antibody and inhibitor for FGF, NT-3, NT-4/5, BDNF, IGF-I/II, NGF, PDGF and estrogen, respectively. MTA (5-deoxy-5-methylthioadenosine) specifically inhibits the self-phosphorylation of FGF receptor in the living cells [P.A. Mather, J. Bio. Chem., 268, 4244 (1993)]. Therefore, the cytoprotective effect of the test compounds is inhibited by treatment of MTA, this effect is depended by the signal transfer effect through the phosphorylation of FGF receptor.

【0153】

The inhibitors of the various kinds of receptor were dissolved in the optimum concentration, and MTA was dissolved in the concentration of 7.5 mM, just before the using. 30 minutes before the treatment of the test compounds, 0.75 mM of each inhibitors or MTA was added, and the cytoprotective effect of the test compounds was determined by mean of MTT method.

The results of each Biological Test 1 and 2 were shown in the following Table 2.

【0154】

【Table 2】

Compound No.	Survival Rate (%) (Compound: 1 μl)	Survival Rate (%) (Compound: 1 μl & MTA treatment)
2	95	20
3	124	19
4	54	25
5	76	32

【0155】

Biological test 3: Evaluation for Calbindin-D-28Kd inducing effect

In accordance with the method of M. P. Mattson [M. P. Mattson, *Brain Res. Rev.*, 13, 179 (1988)], brain of 18-days fetus rats of Wistar strain was taken out. Then, cells of cerebral cortex (5,500 cells/mm^2) were seeded on poly-L-lysine coated 6 wells plate (Falcon) (3.5 mm, Sumilon) and incubated for 7 days.

Test compounds were added 5 days after initiation of the incubation, and after 7 days of incubation, the protein was extracted with homogenized buffer solution [containing 20 mM of Tris-HCl (pH=7.4), 1 mM of EDTA, and 0.1 mM of phenylmethyl-sulfonyl fluoride]. The effect of the test compounds was determined by the western blot technique using polyclonal anti calbindine-D-28K Swant (Swant Co., Ltd.) as antibody. Table 3 shows the test results. In the table, the amount of induced calbindine-D-28Kd of the control group (none-treated group) was indicated as 100 percents.

[0156]

[Table 3]

Compound No.	Amount of induced Calbindine-D-28Kd (% vs. control) (Compound: 1 μM)
4	122
Control	100

[0157]

Biological test 4: Evaluation for cytoprotective inhibiting effect by antisense oligonucleoride

It is necessary to produce the protective protein for the signal transfer action of cells through the phosphorylation of FGF receptor for the cytoprotective effect of the test compounds, and the calbindin-D-28Kd is one of that protective proteins having Ca^{2+} buffering function. Therefore, the following test determined whether calbindin-D-28Kd is concerned in the cytoprotective effect of the test compounds by using an antisense

oligonucleotide.

The brain of 18-days fetus rat of Wistar strain was taken out. Then, cells of cerebral cortex (4 x 10^5 cells/ml) were seeded on poly-L-lysine coated 96 wells flat bottom plate (Sumitomo Bakelite Co., Ltd.) in concentration of 4 x 10^4 cells/each wells. From 2 days after the incubation to 8 days, each 5 μM of Neurobasal medium and three kinds of antisense oligonucleotides were added respectively, on every 24 hours. 7 days after incubation, 1 μM and 10 μM of the test compounds were added, and 8 days after incubation, 300 μM of glutamic acid was added. Then, frther 12 hours after adding of glutamic acid, MTT [3-(4,5-dimethylthiazol)-2,5-diphenyl-tetrazolium bromide] was added, and incubated for 6 hours.

After incubation, dimethy sulfoxide was added to each wells, and the amounts of reduced MTT were colorimetrically analyzed by Micro ELISA Reader using 570 nm of main-wavelength and 650 nm of sub-wavelength.

The effect of the test compounds was determined as the survival rate of living cells (%) according to the equation as indicated in the Biological Test 1: That is, the survival rate of living cells after incubation of the control group was converted to 100 %, and the survival rate of living cells of the tested compounds was calculated.

【0158】

The sequences of the antisense aligonucleotides to be used in this test are following.

calbindin antisense 1: 5-TGA CTG CAG GTG GGA TTC TGC-3

calbindin antisense 2: 5-ACC GTC GAA ATG AAG CCA GA-3

calbindin antisense 3: 5-CGT ATC ATC CAC GGT CTT GTT-3

【0159】

Biological test 5: Evaluation for cerebral edema suppressing effect

8-week-old rats of slc : Wistar strain were used. Rats were anesthetized by intraperitoneal administration of 50 mg/kg of Nembutal (Trade Name), and then, fixed on brain fixactor. The sterile metal screw (3.75 mm in length / 1.0 mm in diameter / 0.75 mm in length of screw thread) was plugged in the 1.5mm right and 0.8 mm rear side of the bregma to press frontparietal cortex organ to cause brain injury. 6 days after the operation, the whole brain was taken out and right cerebral hemisphere (injured side) was isolated. After measurement of the wet weight of the cerebral hemisphere, it was dried at 110°C for 24 hours on aluminum foil. The dry weight of the cerebral hemisphere was measured, and the water content was calculated by using the following formula: Water content (%) = [(wet weight of hemisphere - dry weight of hemisphere) / wet weight of hemisphere] x 100. The test compounds were intravenously administered just after the operation via tail vein of the rats. Table 4 shows the test results.

[0160]

[Table 4]

Compound No. (administration amount)	Cerebral edema suppressing rate (%)
4 (3 mg/kg)	24.9

[0161]

[INDUSTRIAL APPLICABILITY]

As described above, the present invention provides lower molecular compounds, especially aminophenoxyacetamide derivatives of the formula (I), which induce the calbindin-D-28Kd, one of Ca^{2+}-binding proteins, and can be easily administrated.

[0162]

Since the induction of calbindin-D-28Kd caused by the administration of the compound provided by the present invention

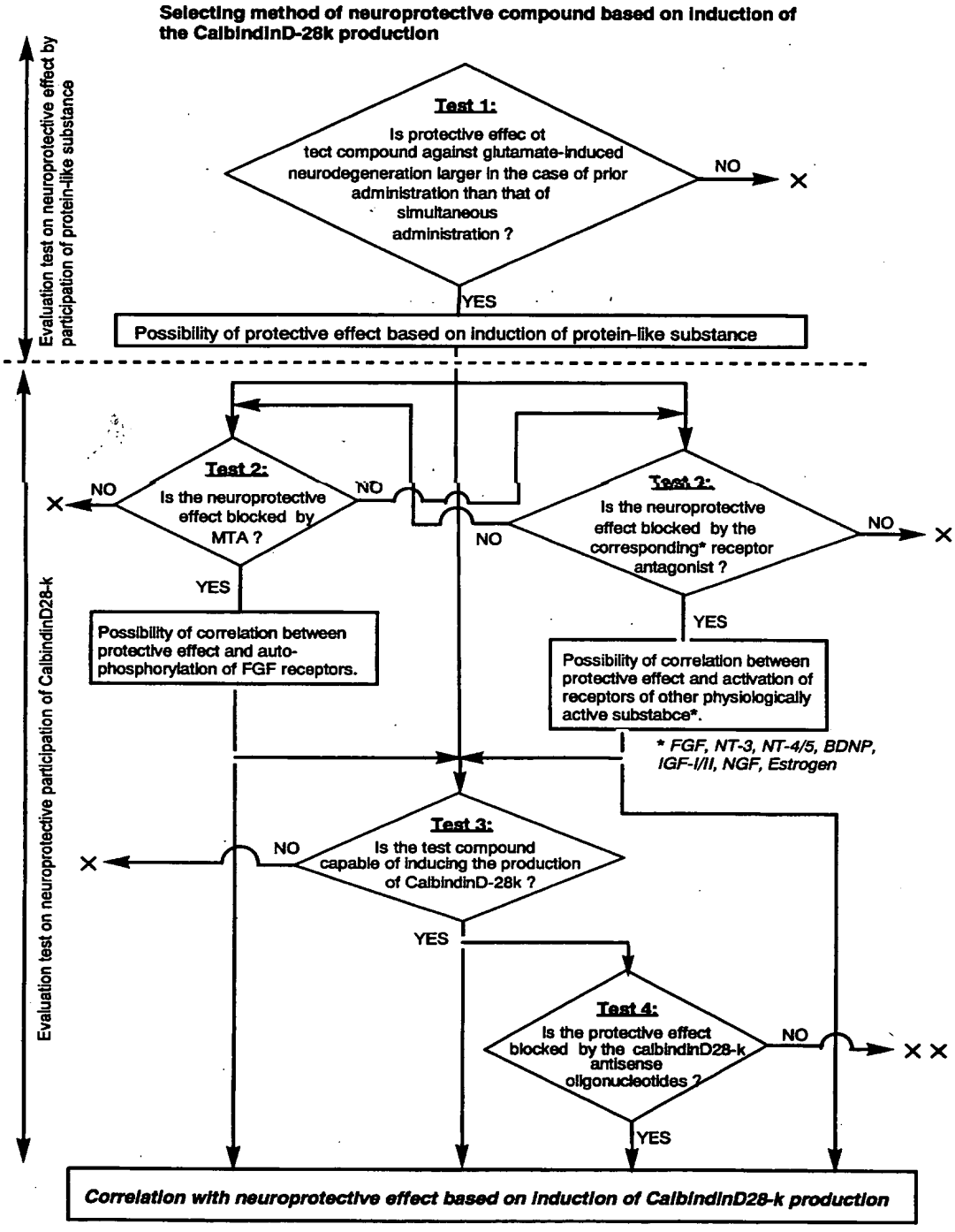
cause neuroprotective effect and cerebral functional and organic disorder improving and treating effect, it can be understood that the agent of the present invention is highly applicable in pharmaceutical field.

【BRIEF DESCRIPTION OF DRAWING】

Figure 1 shows the flow chart of the selecting methods of lower molecular compound possessing neuroprotective effect based on production increasing effect of calbindin-D-28Kd of the present invention.

【Name of the Document】 Figure

【Figure 1】



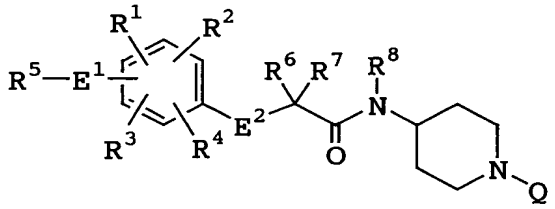
×: Compound out of selecdtion.
××: Compound produces CalbindinD-28k, but main neuroprotective effect is correlated with something else.

【Name of the Document】 ABSTRACT

【Abstract】

【Purpose】 The present invention relates to cerebral functional or organic disorder improving and treating agents containing aminophenoxyacetamide derivatives and pharmaceutically acceptable salt thereof having neuroprotective effect by introducing calbindin-D-28Kd, one of Ca^{2+}-binding proteins, as an active ingredient, and to the methods for selecting these aminophenoxyacetamide derivatives. These compounds have neuroprotective effect and cerebral functional and organic disorder improving and treating effect.

【Means to solve the problem】 There is provided an aminophenoxyacetamide derivative of the following formula (I):



(I)

wherein, R^1 to R^4 are, independent from each other, hydrogen atom; halogen atom; hydroxy group; alkoxy group, optionally substituted alkyl group or optionally substituted aryl group, etc.; E^1 and E2 are oxygen atom, sulfur atom, etc.; Q is $-(CH_2)n-X-Y-Q'$ (n is integer 0 to 5; X and Y are connecting bond; alkylene or alkenylene group, etc.; Q' is pheny, phenoxy, benzoyl, pyridyl groups which may be substituted, etc.),
or a pharmaceutically acceptable salt thereof.

【Selected Figure】 Figure 1

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[List of the Documents]

[Item]	Specification	1
[Item]	Figure	1
[Item]	Abstract	1

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